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Monthly Message

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To one who has intimate knowledge of the Marines in World War I, who was associated with them in the landing operations in Southern France in World War II, and who visited their front lines in Korea in the winter of 1951, it is obvious that neither the officer nor enlisted corps needs any defense but rather are to be commended for their high esprit and cooperation with and support of each other.

Frank B. Berry

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Assistant Secretary of Defense
(Health and Medical)

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Foreword

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REAR ADMIRAL BARTHOLOMEW W. HOGAN,
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Surgeon General, United States Air Force.

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ECOLOGY OF DISEASE IN WORLD HEALTH

JACQUES M. MAY, *M. D.*

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At the outset of this talk I would like to state that its purpose is to define the new concept of medical ecology and to show how its study is essential to understand the world health problem.

The student of medical ecology and disease geography, two closely related fields, is confronted with two possible approaches: He may consider political units first—unfortunately, statistics do not come by geographic regions—and explore disease occurrence in these units after; or he can take one disease at a time first and build a global picture of its extension throughout the various regions of the world after.

Dr. Simmons and his associates in their book, *Global Epidemiology,* used the first of these two approaches, and started their presentation of disease distribution with a description of the

Annual James Stevens Simmons Memorial Lecture presented at Walter Reed Army Medical Center, Washington, D. C., 16 January 1958. Dr. May is Head, Department of Medical Geography, American Geographical Society, Broadway at 156th St., New York, N. Y. He also is on the staff of New York University College of Medicine and is a visiting lecturer at Harvard University School of Public Health.

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geographic layout, followed by a study of disease occurrence in the area. This is a very useful and convenient approach, especially for the public health researcher who knows where to look for data he needs in each country.

The second approach, taking one disease at a time, and building the map of its extension throughout all the regions where it is known to occur, is the approach that we have used in compiling our *Atlas of Diseases*. This method has advantages for the epidemiologist who wishes to explore the reasons for disease occurrence. Once possessed with a map of disease, the study of the environmental and cultural factors that are present throughout the area of occurrence reveal the minimal requirements needed for the disease to exist.

These requirements can then be investigated on a world-wide basis and a comparison of their respective importance in various places becomes possible. Both approaches, of course, complement each other and they are both indispensable to understand the ecology of disease.

DEFINITIONS

I am using the words "ecology of disease" knowing full well that they are controversial. But controversy is the basis of intellectual life, and I do not feel I should make an apology for throwing around an idea because it arouses controversy.

A friend of mine, a distinguished practitioner in the city of New York, remarked to me one day, "Why do you always use this word 'ecology'? Nobody knows what it means." More recently my friend Gurney Clark, head of the Department of Epidemiology of Columbia University, told me that he preferred the term "natural history of disease." As Gurney knows the meaning of the word ecology, his criticism impressed me much more.

Another critic agreed that there are ecological problems involved in medicine, but doubted whether one should speak of the ecology of diseases. "One can conceive," he said, "discussing the ecology of a living thing, a plant or a vector, but not of a phenomenon such as disease." My answer to these critics is that the word ecology means the science of the habitat, of the home, and that it connotes the idea of "focus," of "nest," as the Russian disease ecologist, Pavlovsky, puts it. This notion of disease having a cradle, a fatherland, a habitat whence it spreads to other areas, is basic to global epidemiology, which is the science that studies all the "nests" or "foci" or homes of disease, and the way they reach areas of the world outside their homes. It is of value to be aware that some diseases have a focus, for example, cholera; that the conditions existing in

this focus are indispensable for the disease to occur; and that outside their foci the disease does not occur unless its factors do a job of adaptation. Thus, I hold that the phrase "ecology of disease," including the idea of focus (which alternate expressions do not include), is worth retaining in our vocabulary.

In order to justify further the title of this presentation, it is needful to go back to basic definitions. What is disease? Up to very recently, the concept of disease had a very individual, very local ring. It meant symptoms and treatment: "One ill, one pill, one bill." This is a legitimate approach of course, but not satisfactory to the public health worker, nor to those who follow Dr. Simmons' teachings, think in a global way, and want to learn more about more, rather than more about less. To the disease ecologist, *disease is that alteration of living tissues that jeopardizes the survival of the individual or of the group in the environment in which it occurs.*

This definition has the advantage of introducing the all important notion of environment. Indeed, normalcy cannot be defined per se. Disease is a relative thing. Further, the same tissue change does not constitute disease everywhere.

Recently, Sir George Pickering, the Professor of Internal Medicine at Oxford, England, took me to task at a meeting, where we were seated together, because I had suggested this definition which he said did not help the practitioner in his daily problems. A few moments later, Sir George was trying to define the boundaries between pathologic and physiologic high blood pressure—what is a normal blood pressure? What could be a criterium for hypertension? Of course, there cannot be an acceptable definition of the normal, so I suggested to him that hypertension becomes pathologic when it jeopardizes the survival of the patient, either on a short-term, or on a long-term basis in the place where it occurred. Being a good sportsman, he had to agree.

The same tissue alteration does not constitute disease everywhere. The Indian living at an altitude above 10,000 feet in the Andes has 8,000,000 red blood cells per cubic millimeter, as well as a higher degree of blood viscosity, a larger heart, and, in general, a lower systolic blood pressure than the man living at sea level. He most probably also has other, as yet not explored, biochemical traits which might be considered pathologic should they occur in a different environment. Perhaps we also can add boldly that the group of people possessing the "S" type of hemoglobin in a malarious environment are not as sick, if they are sick at all, as the same group would be in a nonmalarious environment.

HOW DISEASE OCCURS

Disease must be understood on an area basis. If disease is recognized to be that alteration of tissues placing persons in jeopardy, which we have just said it was, what are the factors needed to bring about such an alteration?

For the convenience of the discussion, we can group under three headings the factors playing a decisive role at a certain place and at a certain time in the occurrence of disease or in the formation of a disease pattern. First, we must have a stimulus from the environment. Second, we must have a response from the host, loud enough to be detected, if not by clinical exploration, at least by using the modern instruments of modern medical technology. The degree of this response, of course, depends upon the amount of stimulus applied in relation to the genetic make-up of the host. Third, the disease pattern is governed by the operation between stimuli and host of this edifice of customs, habits, and technics that we call culture.

These traits either bring stimulus and host together, thus creating the chance for disease occurrence, or keep them separate, thus preventing the disease. When this happens, there is, at the place considered, a disease potential that is replaced by actual disease if and when the cultural trait separating stimulus and host breaks down or disappears. It is on this three-cornered basis—stimulus, host, and culture—that the science of the ecology of disease is established. It is the study of these disease factors, their geography, their mapping, that gives us our understanding of disease occurrence on an area basis and forms the structure of a "global epidemiology."

ENVIRONMENTAL STIMULI

Physical Stimuli. First among them are the so-called physical stimuli, those that geographers include in their definition of climate. Few physicians realize that we know extremely little about the influence of these physical climatic factors on man as a host. Dr. Douglas K. Lee,[1] formerly of Johns Hopkins, and now with the Quartermaster General, established an interesting diagram based on the combined plotting of temperatures, in abscissas, and humidity expressed in vapor pressure, in ordinates. Within this area Lee defines several zones: a zone of comfort below or beyond which nobody is comfortable, a zone where muscular performance begins to deteriorate, a zone where mental performance deteriorates, and a zone of distress. It is possible to superimpose on this chart another chart based on the range of mean monthly temperatures and humidity for sample locations. Thus it can be seen how the people of Rio de Janeiro, or Basra fare in comfort or discomfort, and under which limits

exertions can be expected from them. Beyond this knowledge, loosely measured by the terms comfort and distress, our gaps of knowledge on the effects of climate on man reach the proportions of an abyss.

The reasons for our ignorance on matters of climatic influence on men is that it is impossible to separate in nature the physical elements of climate from the living things that have established their habitat in these climates. When our grandfathers used to speak of good or bad climates they meant climates where no outside aggression attacked the body, or climates where such aggressions occurred. What they considered to be climate, essentially meant the disease agents that unknown to them existed in these climates. When climates are reproduced in artificial chambers, the result is a distorted picture, because many unknown elements existing in the outside world, such as heat and humidity, are not present among the variables.

We are just beginning to realize the existence and possible importance of such unknown variables as cosmic rays, static electricity, radiations, and probably still other material forces that have no name. If it is possible that flares in the sun may disrupt what I might call "macroscopic" electronic communications on earth, then it is likely that they also may produce changes in the "microscopic" electronic communications that occur in things around us and in ourselves, and probably are intimately involved in the make-up of what we call life.

The forces of climate conceivably may influence our resilience to disease in an indirect way, the same as they do in the chicken. We all remember Pasteur's[2] experiment with anthrax, which he was unable to induce in his chickens until he lowered their body temperature by plunging them in an icy bath, after which the inoculation was successful. The condition of stress, as we called it, for lack of a better understanding of what happened, created in the chicken a susceptibility of disease that had not existed before.

Further, the physical elements of climate, those we know how to measure and those we don't, influence the things we eat and the agents, vectors, intermediate hosts, and reservoirs that bring us our transmissible diseases. The whole field of climatically induced mutations in agents, vectors, and hosts is practically unexplored.

To a large degree, these physical elements of climate also govern men's cultures, from the material that is made available to build human dwellings to types of architectures, diets, and means of transportation. The air, the water, the earth, and the temperature, govern what happens to places, as good old Hippocrates could have said, and thus govern the disease pat-

terns. So far, we physicians have done little to explore the fields of geology, geography, climatology, meteorology, and physics with the purpose of relating the findings of these sciences with disease occurrence. My humble contention is that more teamwork between disciplines is needed along that line and would repay a large amount of dividends in knowledge.

Biological Stimuli. The second group of stimuli challenging human survival comprises all the living things who have elected to inhabit the various "niches," as ecologists say, the "macro" and the "micro" climates. An important aspect of the coexistence agreements developed by these living things, which the physician and even the public health worker often forgets, is that these living things, like men, live in societies. Here I have to bring you a definition of what the medical ecologist understands by the word "society." *A society is a pattern of mutual tolerance that occurs temporarily among living things when the dynamism of reciprocal exclusion has been exhausted.*

The idea in these condensed words is to stress that a social structure is essentially temporary, based on mutual tolerance. A mutual tolerance implies dominance and submission, and the moment anything happens to disturb the equilibrium of this pyramid, of this compromise, the pattern is upset, new dominants come to the top with unpredictable results. The reason for all this, of course, being that, whatever size they are, infinitely small, or tremendously big, living things always compete for food and shelter.

I believe that it is profitable for the medical ecologist, studying the occurrence of transmissible diseases throughout the world, to remember that in all likelihood, bacterias—and who knows, perhaps also viruses—snails, mosquitoes, rodents, and mammals, all live in society. It is on this concept that the modern therapy by antibiotics, and in many instances, disease control, is based. Indeed, in a room loaded with an aerosol of *Penicillium notatum,* the transmission of pneumonia among human hosts would not occur for lack of a live pneumococcus; in a paddy field, sown with gambusia, *Anopheles jeyporiensis candidiensis* would have a tough time really surviving, and so would *Plasmodium vivax* for lack of adult mosquito habitat in which to spend its sexual life.

It has been shown that it was difficult to have yellow fever virus multiply in an *Aedes aegypti* previously fed on dengue virus.[3] Could it be that these two viruses do not belong to the same social structure in spite, or because of, their relationship? These social structures of living things are closely de-

pendent upon the geographic factors and the food availability discussed above, which is why we find these societies closely integrated and almost identified with the various geographic areas in which they occur.

RESPONSES FROM THE HOST

I particularly wish to discuss now the global epidemiologist's approach to the study of this response from the host. There is very little known on this subject; we have paid scant attention in the past to this host. Our textbooks and our literature are full of studies on the living stimuli but offer very few on the host's structure, on the genetic make-up of the man who presents the symptoms, and on the relationship between genetics and biology.

We have, so far, not been able to manage any classification of hosts on the basis of their response to environmental stimuli. We have no map of susceptibilities and immunities. The psychiatrists are the worst offenders along those lines. They have concentrated so much on the study of the stimuli, conscious and unconscious, that they have almost completely forgotten the patients, and they speak of functional versus organic disorders as if anything functional could occur in a vacuum and could be understood without an exhaustive study of the physical structure supporting it. I believe that the medical ecologist can make an important contribution to the understanding of disease, any disease, by showing that as much attention must be given to the study of the host as is given to the study of the stimulus.

What lies at the basis of the response any individual or any group offers to environmental challenges? Obviously, the genetic make-up. We all know that the genetic make-up of an individual is represented by the sum total of his genes (his genotype), and by the appearance of his genotype at a given time (his phenotype).

If it is true that the concept of "one gene—one enzyme" has value, then we can understand why certain people or animals are susceptible to certain diseases and others are not. Why is leprosy essentially a human disease and why is foot-and-mouth disease essentially a cattle disease? Why do cholera vibrios multiply in the intestines of guinea pigs without causing them any harm? Why can't birds catch human malaria? The enzymes governing these agent-host relationships are there or not; the genes that support them are present or not.

All these problems underline the considerable importance of the terrain. We recently have been given interesting hints along these lines. Some studies seem to indicate that individuals

belonging to blood group "O" are particularly susceptible to the stimuli that result in the development of peptic ulcers.[4] The role of the so-called hemoglobinoses in shaping the responses to pathogenic stimuli is certainly worth exploring thoroughly. We don't discuss any more the fact that the sickle cell trait protects against *Plasmodium falciparum*;[5] we have reached the stage where we seek to understand how. It would be of great interest to find whether hosts having the Kell system or any other system in their blood, and who belong to this or that blood group, are not more susceptible to this or that disease than hosts with another genetic make-up. All this seems to outline an important field of investigation for the future.

The genetic establishment of an individual or of a population is more closely linked with the environment than we currently realize. The genotype of a population is what it is and becomes what it shall, because of the presence of environmental stimuli and pressures that cause *mutations* and force living things into *migrations*. Mutagenic factors are little known; however, heat, chemicals, radiations, and probably others are specific to their environmental niches. The way they combine gives the macro or micro climates in which things live, their characteristics. These climates exert their influence on the genes of vegetables and animals alike, causing mutations that upset the social patterns referred to above, causing dominants to lose their dominance and submissive elements to acquire dominance.

When we say this year was a bad year for cholera, there was too much heat and humidity, we may be giving only a partial description of what occurred, because it could very well be that the cholera vibrios living in that area have mutated from a mild strain into a virulent one through the effects of heat, humidity, or radiations. This, of course, can also be true of the influenza virus and of any other agent, vector, or reservoir we can think of.

When the environment exerts its pressure, and when this pressure gets to be too painful for any living group to accept, the group usually flees that environment. This occurs when animals migrate, and when European populations come to America to escape political pressures in the old continent. The result of these migrations at every level, from disease agents to man, are to mix up genes and to create a new genotype in the particular environment to which these biotic refugees have fled. Thus it is justified, from the genetic angle as well as from all others, to link the disease pattern with geographic pressures.

As for the phenotype, its relation to the pressures of the environment are only too obvious. Genetic material is like a pellet of clay of a certain weight, mass, and density. This we

can shape into the figure of a woman, a horse, or anything else. It is still the same pellet of clay with the same weight, the same chemical structure, the same genotype; however, under the pressure of the environment (in this case, the fingers of the artist) the phenotype looks like a woman or like a horse.

In the same way, the environment in which man lives, pressuring his genotype, brings about new shapes, new phenotypes that may be useful for continuation of living in that same place, or that can be detrimental. If a man has lived for a certain time in a certain environment, he has been bitten and hurt, and has suffered emotions that are specific to the place. All these stimuli have left scars, the sum of which form his personality and govern his future response to further stimuli. Some of these scars are beneficial (immunities and education), some are detrimental (allergies and neuroses), and it is the total of these scars that governs the disease pattern by governing responses to the stimuli present in the environment.

CULTURAL FACTORS

The third group of forces that intervenes in the disease pattern is the culture of the various human groups that grow in the infinite variety of physical and biological environments. Here we come to the definition of a word that the medical ecologist has to use repeatedly; this word is "culture." *To the global epidemiologist, culture is the sum total of the concepts and technics that individuals or populations use in order to survive in a given environment.*

That, of course, does not mean that all cultural traits are survival-worthy, if I may be forgiven for the use of a barbarous word. It is quite possible that many cultural traits will lead the group to its destruction rather than to its survival. A case probably could be made to show that originally these traits have developed because they were mistakenly thought to promote survival or because they did promote survival at the time when they were adopted, but have ceased to do so when circumstances changed. People do not give up their culture easily, they like to feel the protection of their ancestors around them, and they would rather die doing something that has always been done than survive by not doing it, or trying something that has not been tried before.

The origin of culture is truly the job of anthropologists, and I am not competent to discuss it. My point of view is that of the epidemiologist; we ecologists of disease are only interested in finding out whether a cultural trait promotes disease or prevents it. My definition of culture has no other object than to help decide when we are confronted with a cultural trait and whether it is helpful or detrimental.

For instance, in Southeast Asia we deal with a population whose culture implies walking barefoot on a heavily polluted soil. We can say that this is detrimental—yet, in certain villages of India, the villagers place wooden boards on the soil of the defecation areas. This reduces the contact between feet and polluted soil, and prevents, to a certain degree, the mixture of earth and fecal matter that is needed for the hookworm larvae to develop. As a result, in such villages, the hookworm rate is much lower than where the defecation area is not protected by such boards.

A similar favorable effect on hookworm disease obtains in China in the areas where the silkworm industry, rather than rice cultivation, flourishes. In these areas, the farmers spend much time on ladders tending the mulberry trees and have much lower rates of hookworm infection than the rice growers.

Yet, culture carries its many threats to survival; often, such threats are a counterpart of developments intended to prolong survival. Such are the many examples of man-made malaria and, in our own culture, the possible role in producing disease patterns of insecticides that seep into the soil and may be recovered in the crops; of butter coloring, with its possible carcinogenetic nucleus; of food preservers; and even just plain excessive eating of fat-producing molecules, which we are persuaded to do by the loudly advertised requirements of our ever-growing industry. Cultural traits also influence disease patterns in many indirect ways. The physical environment not only shapes societies of living things, as we have seen, but it also shapes cultural patterns and hence the diseases that arise within these patterns.

The example of the farmers in northern Vietnam is interesting. These people live in one of the two or three most densely crowded areas of the world. The density of population is around 900 per square mile. The houses and the villages they form, represent, from the point of view of the way they are built, a compromise between the material that is available and the need to save as much soil as is possible for food crops. The material available is mud and rice straw, which does not lend itself to sky-scraping architecture. Thus, there are very few two-story houses in the villages of the Red River Delta. The dwelling place usually consists of a mud bungalow with the pigsty on one side and the kitchen on the other. Please note that there are no fierce malaria vectors in the area.

Some sixty miles to the north, in the hills, we find a different cultural trait, also very much influenced by the physical environment. In these hills lumber is abundant, but there is little rice straw and little mud. The people, for reasons that are not

fully understood, build their houses on wooden piles, which places what we would call their living room at an elevation of 12, 15, or sometimes 20 feet above the ground.

In these hills, *Anopheles minimus,* a very fierce malaria vector, abounds, its breeding enhanced by the network of hill streams. However, it so happens that *Anopheles minimus* does not fly much higher than 10 feet above the ground. As a result, although it is essentially a man-biting insect when it has a chance, it feeds on the cattle herded under the house between the piles, because that is what it finds at its normal flight altitude. Furthermore, the cooking takes place in the house, not outside as in the delta; this fills the living room with smoke that chases away any stray vector.

Due to the congestion in the delta, several schemes have been carried out at different times in history to try to relocate delta people in the hills. These people carried their culture to the new location and started to live at ground level, to cook outside the house, and to shelter their pigs away from their dwelling. The results have been disastrous. Malaria epidemics decimated the newcomers, and the reputation of the hilly region among the lowland dwellers is that it is full of evil spirits and that no man of the delta should ever go to the hills.

When we started this discussion, we said that disease occurred when three orders of factors converged, or were present at a certain place, and at a certain time: stimuli from the environment, cultural factors, and a response from the host.

THE ECOLOGY OF DISEASE

The ecology of disease governs our understanding of world health because it is based on the study of the three main chapters we have outlined in this discussion: (1) geographic study and mapping of pathogenic stimuli and factors of disease; (2) geographic study and mapping of the genetic characteristics of the host, taking notice of the known immunities, susceptibilities, and biochemical and physiological traits; and (3) geographic study of cultural traits linking together or separating stimulus and host.

Many concrete examples of what is stated above could be given. It is obvious that it applies to transmissible diseases, but it also applies to noncommunicable diseases. The problem of world hunger is a good example. It is fairly easy to discover where people are starving or suffering from malnutrition. We know how important this problem is in our days, and our country has not turned its back to it, but it is not sufficient to know

that two thirds of the world's population does not eat to its satisfaction, nor is it sufficient to know where these starving people can be found. What we want is to find out why they are starving, and what are the circumstances of human ecology that in each place create the want. If we do not know the constitution of these different pictures throughout the world, our help will be ineffective and wasted.

In some countries malnutrition is the result of scarcity, there is not enough food for the number of people to be fed; or the food is of poor quality, short of the molecules the tissues of the host need and want. In other countries the problem is cultural. In certain parts of India and Southeast Asia the social structure of the society is a serious cause of food shortage; the customs governing inheritance divide and subdivide the land to such a point that it is not soundly workable.

In Mexico, in certain parts of Africa, in the Caribbean Islands, and again in India, there is a competition between men and animals for the food that can be produced, so both starve. In other places, food resources are not used as they should be; for instance, in the Lake Chad region, cattle are currency, a sign of wealth, a local means of exchange. Eating a cow would be like eating one's capital. Little is done to increase milk supply. The food possibilities are not exploited as they should be.

In Brazil, the transportation facilities are inadequate; food cannot be brought from one province to another when needed. In Colombia, except for the Magdalena Valley area, a peculiar setup leads to semistarvation: Much land is used as a security against inflation, not as a good producer. Good land is used for cattle grazing on an inefficient basis, while most food crops are grown on small farms, often on steep slopes and in poor soil.

Elsewhere we find that cultural taboos play a role. People starve in Bengal rather than kill a cow, or even eat the flesh of one that has died. In some other places, especially in South America and in North Africa, hunger is fostered by absentee ownership of large estates where tenants raise cash crops instead of food. In some places, again as in India and China, you find, combined together, population pressures, exhaustion of arable land, poor farming technics, cultural taboos, poverty, social and economic restricting cultures, and lack of capital.

The occurrence of deficiency syndromes also may be influenced by the genetic make-up of the host. There is some evidence that certain Polynesian groups thrive on diets that would

be unsatisfactory to Caucasians.[6] Do their genes provide them with the power to synthetize amino acids which the Caucasians have to find ready-made in their diets?

THE CHANGING MAP OF DISEASES

I should like to add a word about the changing map of disease and the changing maps of disease factors. These maps have to change. First, because the environment changes; as alluviums fill up estuaries, isolated villages are replaced by large cities. The diseases that were prevalent among the sparse population of Manhattan when Captain Hudson came sailing to our shores, are not the same as those that prevail today at the same place. When jungles are cleared, as in parts of Malaya, or are allowed to reconquer the land, as on the site of the dead city of Angkor, new societies of agents, vectors, and hosts nestle themselves in the new niches. Each culture brings about its set of diseases.

It would be of great interest, if data were available, to write a study of the disease patterns that have accompanied cultures that have run their course and are no more. Whenever possible, history of medicine should focus on the relationship between disease patterns, as far as they can be ascertained, and the climatic, biologic, and cultural niches in which they were established. Example: We have just begun to open the chapter on the diseases of radiation.

The map of diseases also changes because of migrations. It is one of my cherished projects to compile a map and to write the attendant discussion on bird migrations. I imagine that such a project would be of interest to virologists.

In conclusion, let me tell you about a cartoon I saw a short while ago. I am sure Dr. Simmons would have liked it because of its implications: It represents an old Chinese couple in some remote village of China. The man is blowing his nose, and the woman says: "Little did you know when you started those few sneezes some months ago that you would become a world figure." Eleven years ago another man became a world figure, his name was Mr. Lebar. We should remember Mr. Lebar because General Simmons introduced his book on Public Health in the World Today by reminding us of the international bus ride that this gentleman took to return to New York from Mexico in 1947. By doing so, Mr. Lebar started a smallpox epidemic that resulted in a huge vaccination campaign in the United States, costing millions of dollars.

Thus at all times the health of tomorrow is prepared and hatched in the remotest corners of the world. We should try to

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keep informed in regard to these events. We should try to recognize the birth of new stimuli to disease, the changes that occur among the social structures of agents and vectors, and the changes in the maps of immunities and susceptibilities. We must keep abreast of the cultural changes that either create new links between agents and hosts, or erect protective shields between them. This we must do if we are to follow the great lines of Dr. Simmons' global thinking, and if we are to live up to the expectations of the world that our country will be a leader in the field of world health.

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ALKYLATING AGENTS: A BRIEF REVIEW

WILLIAM McFARLAND, *Commander, MC, USN*

CHEMOTHERAPY of the leukemias and related diseases has advanced considerably since 1942, when in the midst of World War II Goodman and Gilman,[1] then at Yale, discovered that nitrogen mustard could substantially reduce the tumors of lymphosarcoma and Hodgkin's disease. For the next few years research into the effects of such agents was classified, and only a few observers[2] made the primary observations that led to the general use of nitrogen mustard in Hodgkin's disease and lymphosarcoma. In recent years, many new "alkylating" agents have been developed, chiefly by Haddow and his colleagues at Chester Beatty Institute in London. A recent symposium of the New York Academy of Sciences[3] was devoted to the alkylating agents, and marked the 15th anniversary of the introduction of nitrogen mustard. The symposium, attended as it was by over 600 observers, may be said to have been a monument in honor of the Chester Beatty group, which has done so much in recent years to develop new agents, some of them, like Myleran (brand of busulfan), having possible selective activity.

Discovered by Ritchie in 1854, mustard gas and related compounds were regarded solely as toxic agents suitable for chemical warfare, and their effectiveness was well documented during Warld War I.[4-6] During World War II there was another demonstration of the effects of these agents, this time quite by accident. The Port Bari incident,[7] in 1943, showed dramatically and tragically the effect of mustard-like agents on humans. At that time the Allies had invaded southern Italy from North Africa, and an important seaport in the chain of supplies was Port Bari, Italy. In the interest of preparedness, a ship was anchored in the harbor containing a cargo of 100 tons of mustard gas, in addition to explosives. On the night of 2 December 1943, a German air raid was particularly effective, sinking sixteen ships and partially destroying four others. The ship containing the mustard gas and explosives was hit directly with loss of all crew members, and the mustard was spread over the harbor,

From the Blood Research Laboratory, William Dameshek, M. D., Director, and Ziskind Research Laboratories, New England Center Hospital, Boston, Mass. Comdr. McFarland is now assigned to U. S. Naval Hospital, Bethesda, Md.

where it mixed with and dissolved in a layer of oil. Those rescued from the water had suffered prolonged exposure to the resulting mustard-in-oil. To make matters worse, because there was no one alive with knowledge of the presence of mustard, this fact was not recognized in the confusion and many of the rescued were allowed to remain in their oil-soaked clothes for 12 to 24 hours. As a result, there were 617 hospitalized casualties from mustard exposure, of whom 83 died. Deaths occurred mainly on the third day, from acute systemic effects of burns, and on the ninth day as the result of pulmonary infections with leukopenia. Of particular interest were autopsy reports describing shrunken spleens with wrinkled capsules. In the few cases where marrow examinations were done, the marrow was described as "pale pink" and "dry."

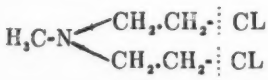
Aside from this dramatic, accidental demonstration of the effects of mustard-like compounds, research work was conducted by selected small groups, as a result of the therapeutic demonstration by Goodman and Gilman. Consistent with wartime security measures, the various mustard compounds were given code letters as follows:

H	–	*bis* (*B*-chloroethyl) sulfide
HN_1	–	ethyl-*bis* (*B*-chloroethyl) amine
HN_2	–	methyl-*bis* (*B*-chloroethyl) amine
HN_3	–	*tris* (*B*-chloroethyl) amine
TL301	–	isopropyl-*bis* (*B*-chloroethyl) amine

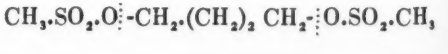
The designation of nitrogen mustard as HN_2 has continued to the present as an abbreviation, with understandable confusion on the part of those not familiar with its origin.

As for the term "alkylating agents," which serves as an all-inclusive term for the various mustard-like compounds, this too may require explanation. According to basic organic chemistry,[1] one example of an alkyl group is an ordinary alcohol minus the -OH group. In the case of methyl alcohol, the alkyl group would then be CH_3-, and in the case of ethyl alcohol the alkyl group would be CH_3-CH_2-, and so on. These groups do not exist as separate molecules, but it is convenient to speak of them as alkyl groups and to refer to their combination with other substances as alkylation. The "mustard" compounds merely contain more complex alkyl groups than the alcohols described; *e. g.*, the formulas for nitrogen mustard and Myleran:

Nitrogen mustard

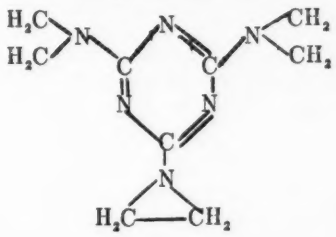


Myleran



The vertical dotted lines show where the compounds react under physiologic conditions to yield alkyl groups capable of biologic activity. Accordingly, the various agents are classified as mono-, bi-, or polyfunctional, depending on the number of reactive groups available. Triethylene Melamine (TEM) is an example of a polyfunctional compound with the capability of reactive alkyl groups in the three ethylene groups:

Triethylene Melamine



The site and mechanism of action of alkylating agents have been the subject of a great deal of investigation. The group working at the Chester Beatty Institute has done much to clarify these matters. According to their observations,[3] the reactive centers of alkylating agents behave as positively charged carbonium ions which have a particular affinity for electron-rich groups in biological systems, such as organic and inorganic anions, amino groups, and sulfhydryl groups. The most important and most common of these reactions appears to involve the primary phosphate groups in desoxyribonucleic acid (DNA). When such a reaction is the result of a polyfunctional agent, cross linkage occurs with marked disruption of the normally straight chain polymers. In other words, the molecule of the alkylating agent with its two or three reactive centers forms an abnormal bridge between different polymers of DNA and even in the same polymer. Such chemical changes occurring in chromosomal material would be expected to produce profound effects on the process of cell division, and this is actually the case.

The reactivity time of alkylating agents appears to be very short, probably within two or three minutes after instillation in a biological system.[3] Excretion studies by Smith and associates[3] at George Washington University, utilizing radioactive tracer technics, indicate that the majority of labeled material is recovered in the urine within 24 hours as a variety of substances, none of which is the unchanged alkylating agent.

Alkylating agents have been termed "radiomimetic" because so many of their effects resemble those produced by x-rays.

Each is capable of suppressing mitosis and producing chromosomal injury. Therefore, each of these agents is capable of producing mutations, some potentially dangerous. Myleran has been shown to produce cataracts in rats[10]—another late complication of radiation (table 1). Of occasional importance clinically may be the fact that alkylating agents are dependent on transportation to the site of activity via the blood, whereas x-irradiation is not. In other words, a large tumor mass with defective blood supply may respond better to local radiation, whereas widespread involvement may be treated more effectively with an alkylating agent.

TABLE 1. *Comparative effects of radiation and alkylating agents*

	Radiation	Alkylating agents
Suppression of mitosis	+	+
Chromosome injury	+	+
Mutagenesis	+	+
Carcinogenesis	+	±
Cataract formation	+	±
Site of action dependent upon transportation via blood	-	+
Action inhibited by AET* and similar compounds[11]	+	+

*Amino-ethyl-iso-thiouronium bromide-hydrobromide.

Hematologic effects of alkylating agents have been studied extensively by Elson of the Chester Beatty Institute. According to his observations,[3] no single agent is completely radiomimetic. For example, C. B. 1348, Leukeran (brand of chlorambucil) has an effect on lymphoid tissue similar to radiation, whereas Myleran's effect is radiomimetic with regard to the granulocytic elements. The simultaneous administration of both agents produces a hematologic effect quite similar to radiation.

From a host of alkylating agents that have been produced and studied, five or six have emerged as effective and useful agents clinically. These are nitrogen mustard, methyl-*bis* (*B*-chloroethyl) amine; Myleran, 1,4-dimethylsulfonyloxybutane; Triethylene Melamine; C. B. 1348 (Leukeran), p-(Di-2-chlorethyl) amino-phenylbutyric acid; possibly TEPA, triethylenephosphoramide; and Thio-TEPA, triethylenethiophosphoramide. In general, the effect of each of these compounds is similar in that they react with actively dividing cells whether in neoplastic tissue, bone marrow,[11] gastrointestinal mucosa, or elsewhere. Yet, there appear to be sufficient differences in selectivity of action to render a particular agent the drug of choice for a particular neoplasm.

Nitrogen mustard has been the most available and therefore the most thoroughly tested alkylating agent, and it is still one of the most useful.[12,13] It usually is the chemotherapeutic agent of choice in Hodgkin's disease and lymphosarcoma and is used frequently in carcinomas of the lung, ovary, and breast. It ordinarily is administered intravenously in a total dose per course of 0.4 mg/kg which may be given at once or in divided doses. It also may be administered intrapleurally or intraperitoneally.

Myleran has become the chemotherapeutic agent of choice in chronic granulocytic leukemia. In this disease its action has been almost completely predictable, allowing for titration of dosage according to the response in the white blood cell count.[14] It may be administered in doses of 4.0 to 12.0 mg daily, initially, and then reduced gradually as the white cell count returns toward normal.

TEM and C. B. 1348 (Leukeran) appear to be more specific against neoplasms involving lymphoid tissue; therefore, they have been used most frequently in chronic lymphocytic leukemia, lymphosarcoma, and Hodgkin's disease.[15,16] Both are administered orally, TEM in a dose of 2.5 mg one to three times weekly, and C. B. 1348 in doses of 2.0 to 30.0 mg daily. Because TEM often is unpredictable in its depressant effect on the marrow, its use is being supplanted by C. B. 1348 in most cases where an oral preparation effective against lymphoid neoplasm is indicated.

TEPA and Thio-TEPA have been used in a variety of malignant neoplasma with variable temporary response, but the most beneficial effect has been in ovarian and breast neoplasms where survival time may be prolonged significantly. The average dose per course of treatment varies widely (20 to 600 mg), depending on whether the agents are administered by oral, intratumor, intrapleural, or intraperitoneal routes (table 2).

That alkylating agents are capable of temporary inhibition of malignant neoplasm, there can be no doubt. But why must their inhibition be partial and temporary? There may be some acquired resistance by persisting neoplastic cells, or the answer may lie in the fact that the action of these agents is not sufficiently selective for neoplastic growth. The concentration of alkylating agent in neoplastic cells that are growing in an exponential fashion is not much greater than its concentration in the bone marrow or gastrointestinal tract, where cells are growing in a "steady state." The result may be that the cells which are growing exponentially are depressed only partially and temporarily, whereas the normally proliferating cells are sufficiently affected to preclude further therapy. The question therefore arises as to

TABLE 2. *Alkylating agent of choice, according to usual order of preference*

Disease	Agent				
	Myleran	Nitrogen mustard	TEM*	Leukeran	TEPA** Thio-TEPA***
Chronic granulocytic leukemia	1				
Chronic lymphocytic leukemia			2	1	
Hodgkin's disease		1	3	2	
Lymphosarcoma		1	3	2	
Advanced carcinoma of:					
lung		1			
ovary		2			1
breast		2			1
Mycosis fungoides		1	2		

*Triethylene Melamine
**Triethylenephosphoramide
***Triethylenethiophosphoramide

whether we have exhausted the possibilities of alkylating agents as cancer chemotherapeutic compounds. This may be the case, but the fact remains that the alkylating agents are capable of producing profound alterations in cell growth, and investigations continue in an effort to render them more selective in action by modifications in structure and combinations with other compounds.

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LABELING OF HAZARDOUS CHEMICALS

"A substantial number of packaged chemicals are not now required by law to identify hazardous ingredients on their labels or to warn users of the dangers of overuse or misuse. A recent survey revealed the sketchy, nonuniform, and generally inadequate pattern of regulations at the state and national levels for informative labeling of chemical products. The survey disclosed that, at the national level, label laws exist for drugs, pesticides, certain caustic and corrosive substances, and narcotics. There are no federal laws for the precautionary labeling of industrial chemicals, household chemicals, or poisons, although regulations for the packaging and labeling of dangerous chemicals and explosives in transit by land or water or via the mails are issued by the Interstate Commerce Commission and the Post Office Department."

—BERNARD E. CONLEY, Ph. D.
in *Journal of the American Medical Association*
p. 2154, Apr. 26, 1958

ASIAN INFLUENZA AT FORT BELVOIR, VA.

Epidemiology and Vaccination

JEROME H. GREENBERG, *Captain, MC, USA*

DURING 1957 Asian influenza appeared at most U. S. Army installations in the United States. The infection first appeared in epidemic form at Fort Ord, Calif., during July, and shortly thereafter at Fort Lewis, Wash. It next appeared at Fort Carson, Colo., in September. At that time, it was believed that epidemic influenza would appear shortly thereafter in installations in the eastern United States, and it was decided to study the disease at a representative training post convenient to this institute.

Fort Belvoir, Va., in addition to satisfying the above requirements, provided a training program in which there was a rapid turnover of students from all parts of the country. It was thought that Fort Belvoir would undoubtedly experience an epidemic of Asian influenza. It therefore was decided to set up a study that would describe such an epidemic, relate complications to bacterial flora, and evaluate the effectiveness of the influenza vaccination program on post. This report will be limited to describing the epidemic and the vaccine evaluation.

THE POST

Fort Belvoir, Va., is a major U. S. Army military installation, located about 15 miles south of Washington, D. C., on U. S. Route 1. The major function of the post is the training of personnel for the Corps of Engineers. All personnel have had some previous military training and, therefore, are not classified as recruits.

Approximately 30 per cent of the post military population are students in advanced training courses lasting from 2 to 16 weeks. These students have already received basic training, and the majority leave Fort Belvoir upon completion of their training. The rest of the post military population are "permanent party" personnel who perform the routine administrative and maintenance operations, participate in the management and training of the students, and engage in other military activities. Permanent party personnel generally remain at Fort Belvoir for much longer periods than do the students.

From Walter Reed Army Institute of Research, Washington, D. C.

The students and permanent party personnel differ in a number of respects, including military experience and the type of activity in which engaged. Of particular interest is the relative proximity of the individuals within each group. The vast majority of students attend classes together and reside in large squad rooms in the barracks. As a result, they are in more or less close contact with each other 24 hours a day. The permanent party personnel are more dispersed both at work and in residence. In fact, many live with their families in private quarters and have contact with other military personnel for only a limited period during the day.

It was thought, in September 1957, that Fort Belvoir would probably experience an epidemic of Asian influenza, especially in view of the rapid turnover of students from widely scattered parts of the country.

COURSE OF THE EPIDEMIC

On 7 October 1957, an abrupt rise in the incidence of acute respiratory disease occurred at Fort Belvoir. Arrangements for the study were not yet complete but were rushed forward, and the study was underway within a few days. As a first step, 13 serologic specimens and throat washings were obtained on 8 and 11 October in order to ascertain the etiologic agent. Twelve of these specimens were later determined to be positive for Asian influenza on the basis of fourfold or greater rise in hemagglutination inhibiting antibodies in the convalescent sera. Two of the throat washings were tested, and both yielded Asian influenza virus.

Immediately upon recognition of the presence of an epidemic, an emergency plan, which the command at Fort Belvoir had prepared in advance, was put into effect. Under this plan, all military personnel suspected of having influenza were immediately removed from their units and either hospitalized or placed on quarters. Hospitalization was accomplished in a specially reopened section of the old station hospital and patients were only admitted or transferred to the new DeWitt Army Hospital if complications, particularly pneumonia, were present. The patients placed on quarters were either sent home, if they resided in private quarters, or placed in barracks especially set up and staffed for this purpose. The speed with which the hospitalization program was put into effect and the efficiency with which the medical service carried it out were believed to have contributed greatly to shortening the length of the epidemic by reducing exposure.

Arrangements were made for the study team to be notified by the medical service of all individuals thus hospitalized or placed on quarters for more than 24 hours. The team also received weekly strength reports for all post units. With this information,

weekly acute respiratory disease incidence rates for all units could be calculated.

The course of the epidemic is shown in figure 1. The sudden sharp rise which occurred on Monday, 7 October, reached a peak on 9 October, then dropped to pre-epidemic levels on the weekend. A similar picture was seen in each of the two following weeks, although at progressively lower levels. The peak attained in the fourth week was within the usual seasonal range.

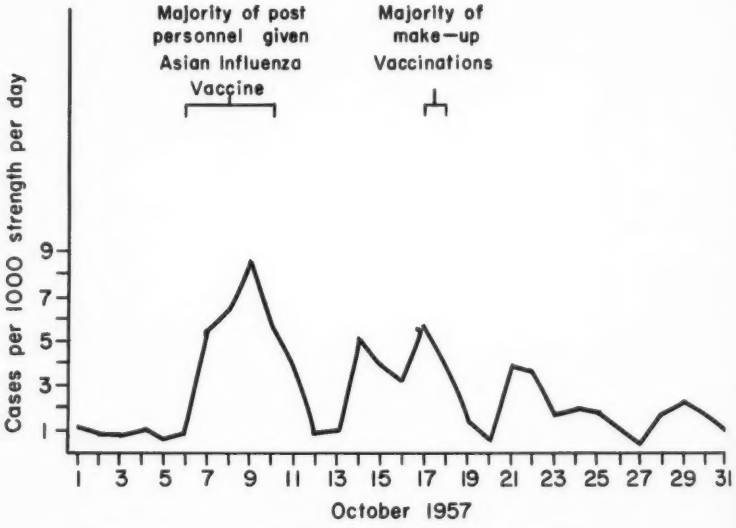
Majority of post personnel given Asian Influenza Vaccine
Majority of make—up Vaccinations
Cases per 1000 strength per day
9
7
5
3
1
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31
October 1957

Figure 1. Acute respiratory disease, Fort Belvoir, Va., October 1957.

Table 1 shows the incidence, in 19 units, of acute respiratory disease necessitating more than a 24-hour absence from duty during the epidemic period. Those units marked "USAECR" (U. S. Army Engineer Center Regiment) and the "USMA Prep School" are student groups, the rest permanent party units. The student units contained approximately 5 per cent nonstudent administrative and supervisory personnel.

Of the 19 units listed, 15 attained their peak incidence in the initial period of the epidemic, 7 to 9 October. The student companies had rates approximately twice those of the permanent party companies for the first three weeks, but by the fourth or fifth week the much-reduced rates were approximately equal.

One student unit, Company A, USAECR, had a rate during the first three days of the epidemic which far exceeded that of any other unit on the post. In fact, this company, which contained less than three per cent of the post military popu-

lation, contributed 20 per cent of the excused-from-duty cases during the period 7-9 October.

TABLE I. — Incidence of acute Respiratory Disease in nineteen representative units of at least 200 mean strength, Fort Belvoir, Va., 7 October–6 November 1957

Permanent Party	7-9 Oct.			10-16 Oct.			17-23 Oct.			24-30 Oct.			31 Oct–6 Nov.		
	Mean Strength	Cases	Rate[1]	Mean Strength	Cases	Rate[1]	Mean Strength	Cases	Rate[1]	Mean Strength	Cases	Rate[1]	Mean Strength	Cases	Rate[1]
1st Eng. Arctic TF	295	2	15.8	295.5	2	6.8	244.5	0	0	201	1	5.0	—[2]	—	—
76th Eng Co	203	4	45.9	208	2	9.6	201.5	3	14.9	—[2]	—	—	—[2]	—	—
H/S, 91st Eng.	217	3	32.2	211.5	4	18.9	232	2	8.6	256.5	2	7.8	227	1	4.4
Cos. A,B,C,D 91st Eng	400	17	99.0	408	22	53.9	422.5	13	30.8	427.5	8	18.7	446	3	6.7
52nd MP	210	2	22.2	210	2	9.5	207.5	2	9.6	206	2	9.7	205	5	24.4
575th Eng	509	5	22.9	502	6	12.0	516.5	1	1.9	529.5	1	1.9	516	0	0
Med. Co. DeWitt AH	517	9	40.6	516	13	25.2	515	11	21.4	516	3	5.8	518	5	9.7
Total	2351	42	41.6	2351	51	21.7	2339.5	32	13.7	2136.5	17	8.0	1912	14	7.3
Student															
Co. A, USAECR	395.5	58	341.7	405	20	49.4	384.5	4	10.4	380	6	15.8	377.5	3	7.9
Co. B USAECR	259	10	90.0	270.5	18	66.5	242.5	11	45.4	232	5	21.6	245.5	0	0
Co. C USAECR	327.5	6	42.7	303	14	46.2	284	7	24.6	292	6	20.5	281.5	8	28.4
Co. E USAECR	371	2	12.6	348.5	3	8.6	360.5	6	16.6	361	7	19.4	324	1	3.1
Co. F USAECR	310.5	6	45.0	315	21	66.7	326	15	46.0	328.5	9	27.4	315	1	3.2
Co. G USAECR	276	7	59.1	278.5	14	50.3	278	8	28.8	264.5	2	7.6	245	1	4.1
Co. H USAECR	279	11	91.9	280.5	15	53.5	287.5	4	13.9	288.5	1	3.5	286	4	14
Co. K USAECR	248	15	140.9	261.5	21	80.3	255.5	24	93.9	250.5	5	20.0	240	2	8.3
Co. L USAECR	289	10	80.6	268.5	6	22.3	265.5	12	45.2	263.5	1	3.8	241.5	3	12.4
Co. P USAECR	222.5	3	31.4	219	1	4.6	213.5	1	4.7	209	2	9.6	211	0	0
Stud. Off. Det. USAECR	866.5	6	16.1	901	12	13.3	922	34	36.9	901.5	12	13.3	877	1	1.1
USMA Prep School	207	5	56.3	225.5	12	53.2	245.5	8	32.6	225.5	3	13.3	226	2	8.8
Total	4051.5	139	79.9	4076.5	157	38.5	4065	134	33.0	3996.5	59	14.8	3870	26	6.7

1 Cases per 1000 mean strength per week
2 Mean strength less than 200

The causes of the exceedingly high rate in this company are not known. The unit had received personnel from Fort Carson, Colo., where an Asian influenza epidemic had been in progress during September. It is probable, however, that other student units had also received personnel from Fort Carson, which is a basic training post and, therefore, one of the chief sources of students. It is likely that there were undetected administrative and social causes which accounted for the high rate in Company A.

The marked drop in acute respiratory disease rates on week ends is of interest and probably indicates that a majority of the cases were relatively mild clinically, hence, could delay their report to sick call for a day or so. The armed services have long been familiar with the week-end decrease in sick visits. This, in most cases, does not indicate malingering during the rest of the week. It does represent either a genuine attempt by the individual to utilize his free week-end time in self-treatment and recuperation or a reluctance to seek medical aid and risk losing the free time. In either event, the individual is usually only mildly ill.

The same degree of illness during the week is often considered by the individual to be incompatible with military training and he, therefore, seeks aid. Frequently his opinion is shared

by the medical officer and he is hospitalized. In addition, some of the mildly ill individuals who avoid the medical facility during the week end are much sicker by Monday and quite willingly report for sick call. This results in the familiar Monday peak. That this was true at Fort Belvoir, is quite evident from figure 1.

VACCINE EVALUATION

A few Asian influenza vaccinations had been given as early as 27 September, but the vast majority were administered in the period 6 to 10 October in a program that was speeded up because of the upsurge in acute respiratory illness. Make-up clinics were then held on 17 and 18 October for new arrivals and individuals who had missed the earlier vaccinations.

As a result of the haste with which the vaccination program was carried out, recording of the individual vaccination was sometimes incorrect or omitted altogether. Because records were deficient, it was found necessary to exclude some individuals from the vaccine evaluation. During the check of the vaccinations it was discovered that despite the efforts of the medical service more individuals had missed vaccination than might normally have been expected. In the two student companies subsequently studied approximately 30 per cent of the personnel remained unvaccinated as of 19 October.

Three student companies of the USAECR and three permanent party companies of the 91st Engineer Battalion were originally selected for vaccine evaluation study because they had high rates of acute respiratory disease. Subsequently one of the student companies had to be excluded from this part of the study because of its failure to report fully its gains and losses in personnel.

MATERIAL AND METHODS

A complete roster of each study company, along with the Asian influenza vaccination status of each individual, was obtained. Arrangements were made for all personnel gains and losses and changes in vaccination status to be transmitted to the study team.

Army policy dictated that all military personnel receive the Asian influenza vaccine, hence, no attempt was made to set up control groups. Previous experience, however, had indicated that there would be an appreciable number of individuals who, for various reasons, would not receive the vaccine, and, therefore, could subsequently be used as a control group of sorts. That the number of such individuals exceeded expectations has already been pointed out. The unvaccinated individuals as a group probably contained no more bias than would have been present in a volunteer control group.

The information obtained from the study companies along with information on cases obtained from the hospital was incorporated into modified life tables. The tables were so arranged that the experience of the groups could be divided into that which preceded and that which followed vaccination.

The analysis was made in two ways. In one, the vaccine was assumed to be effective immediately, while in the other the vaccine was assumed to be effective four days after administration. The effect of these assumptions is to penalize the vaccinated group inasmuch as antibodies against influenza do not usually develop to protective levels until about a week after vaccination.[1]

It has been pointed out that the incidence of Asian influenza, assuming from the initial laboratory results that the majority of cases were of this disease, was twice as high in students as in permanent party personnel during the early weeks of the epidemic, while with the waning of the epidemic the residual acute respiratory disease became equally distributed. The degree of proximity could have contributed to this difference. A major factor, however, was the time and completeness of vaccination. Because the student companies were vaccinated later and less completely than the permanent party companies, there were more unprotected individuals in the student companies at the height of the epidemic.

In preparing table 2, the vaccine was considered to be effective immediately upon administration. Both student companies and one of the three permanent party companies show evidence of vaccine protection, even with this unlikely assumption. The other two permanent party companies show higher rates for the vaccinated than for the unvaccinated.

An analysis has been made in table 3 allowing a four-day delay following vaccination before the vaccine was effective. With this more reasonable assumption it is possible to demonstrate protection in all five companies. Under these conditions, the acute respiratory disease rate in the unvaccinated group exceeds that of the vaccinated group by more than three and a half times in the students and one and a half times in the permanent party.

The occurrence of higher rates in the vaccinated than in the unvaccinated personnel of two of the permanent party units can be explained on the basis of time of vaccination. Almost all of these men were vaccinated at the height of the epidemic. Thus, many cases occurred in these personnel before vaccine protection developed. By delaying the transfer between groups for four days many more cases are retained in the unvaccinated group, thereby elevating its rate above that of the vaccinated and eliminating the previous unlikely relationship.

The use of the arbitrary four-day interval for the development of vaccine protection resulted in lower disease rates among the vaccinated in all five study companies. However, in the

TABLE 2.— Incidence of acute respiratory disease in five companies at Fort Belvoir, Va., 7 October—6 November 1957, based upon the assumption that the Asian influenza vaccine was effective immediately

	Student			Permanent Party			
Vaccinated	Co. A USAECR	Co. K USAECR	Total	Co. B 91st Eng.	Co. D 91st Eng.	H/SCo. 91st Eng.	Total
Person-days	6115	2717.5	8832.5	3941	5620	5122	14683
Cases	24	9	33	13	34	11	58
Rate (Cases per 1000 person-days)	3.9	3.3	3.7	3.3	6.0	2.1	4.0
Unvaccinated							
Person-Days	3458	3937.5	7395.5	1447.5	256	1304	3007.5
Cases	61	42	103	7	1	1	9
Rate (Cases per 1000 person-days)	17.6	10.7	13.9	4.8	3.9	0.8	3.0

TABLE 3.— Incidence of acute respiratory disease in five companies at Fort Belvoir, Va., 7 October—6 November, 1957 based upon the assumption that the Asian influenza vaccine was effective four days after administration

	Student			Permanent Party			
Vaccinated	Co. A USAECR	Co. K USAECR	Total	Co. B 91st Eng.	Co. D 91st Eng.	H/SCo. 91st Eng.	Total
Person-days	5345	2270.5	7615	3362	4874	4501.5	12737.5
Cases	19	7	26	9	24	8	41
Rate (Cases per 1000 person-days)	3.6	3.1	3.4	2.7	4.9	1.8	3.2
Unvaccinated							
Person-Days	4228	4384.5	8612.5	2026.5	1002	1924.5	4953
Cases	66	44	110	11	11	4	26
Rate (Cases per 1000 person days)	15.6	10.0	12.8	5.4	11.0	2.1	5.2

unvaccinated groups the effect was to raise the rates in the permanent party companies while lowering them in the student

companies. This apparently ambiguous result is also explained by time of vaccination. The transfer in the permanent party group occurred early in the epidemic and affected relatively more cases than in the student group where the transfer occurred later when the epidemic had already lessened in severity.

CONCLUSIONS

While the absence of adequately controlled conditions during this study prevents the establishment of scientifically acceptable conclusions, the results do yield impressions to which some significance may be attached.

The acute respiratory disease incidence rates of unvaccinated personnel exceeded those of vaccinated personnel in all study companies, when four days was allowed for the development of vaccine protection. Inasmuch as the epidemic was shown to have been caused by the Asian influenza virus, in the absence of other common factors, the vaccine may be considered to have been responsible for the difference.

SUMMARY

An epidemic of Asian influenza occurred at Fort Belvoir, Va., in October 1957. It began at approximately the same time as the Asian influenza vaccination. A study of disease incidence and vaccine efficacy in recruit and permanent party personnel was made, using the large number of inadvertently unvaccinated personnel as controls.

The duration of the epidemic was approximately a month with the peak occurring in the first week. A rapidly effected and efficient program of hospitalization undoubtedly contributed to shortening the epidemic. Student acute respiratory disease rates were double those of permanent party personnel during the epidemic and approximately equal thereafter. Depression of the rates on week ends was marked.

Vaccine protection was suggested in the five units studied, even though the data was arbitrarily arranged so that inadequate time was allowed for the development of antibodies following vaccination. Acute respiratory disease rates in the unvaccinated student and permanent party groups were more than three and a half and one and a half times respectively those of the vaccinated groups.

The higher degree of protection in the student than in the permanent party personnel was considered to be due to differences in time of vaccination. The higher over-all rates in the

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students were considered to be due to greater exposure resulting from the closer proximity of the students to each other.

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ARE REFERENCE LISTS NECESSARY?

"Opinions among authors and readers vary concerning reference lists appended to scientific articles. The scientific editors are practically unanimous in agreeing that they mean little or nothing to average readers; rarely are the lists desired by teachers and specialists for filing purposes. Some authors are sensitive about publication of references—especially when they contain their own names from one to many times! The lists imply that the author has studied each item and has digested and recorded the "pearls" for benefit of his readers. However, many authors will admit that a conscientious secretary has plucked them from the *Cumulative Quarterly Index* or elsewhere. Incidentally, the term "references" properly means articles actually used in composition of a manuscript. "Bibliography" supposedly means a complete or exhaustive list of published monographs or books upon the subject. In either case, more than a few items upon a list comprise a space-consuming expensive exploitation of the printing trade—at least in a journal like this one which serves a large territory and mostly general practitioners who want the mental pabulum boiled down."

—EDITORIAL
in *Rocky Mountain Medical Journal*
p. 1005, Oct. 1957

THE ADOLESCENT—A MEDICAL MISFIT

FREDERICK C. BIEHUSEN, *Major, MC, USA*

NO OTHER age group has received as little special attention as the adolescent. This important period of our lives is either omitted or glossed over in medical school. The average residency in both pediatrics and internal medicine serves the physician in training to no better advantage. Only recently has a medical school offered a postgraduate course in "Adolescent Medicine."[1]

Adolescents are an in-between age group who fit neither into pediatrics nor internal medicine. The average physician has little interest or knowledge concerning this fascinating time of life. This is true in military medicine as well, where the sharp line of demarcation, the fourteenth birthday, will one day place the adolescent in the pediatric clinic (for which he thinks he is already too old) and the next day in the medical clinic (about which he may have apprehension because he sees few his own age).

The ideal answer would be a clinic the adolescent could call his own, where he would be treated as an individual in a kindly and interested atmosphere.[2,3] It is likewise true that, in time, we should strive for separate adolescent inpatient units as well to provide well-rounded medical care.[4]

THE NATURE OF THE ADOLESCENT

The adolescent is preoccupied with himself and his problems. He resists those who try to direct his life, yet is vulnerable to the person who shows interest, and responds with frankness and co-operation if he believes that genuine interest is being shown on his behalf.

Characteristically these young people show concern about growth and development; feel the need to be popular; show beginning criticism of adults and their behavior; feel a need for success, and a new realization of religion; look for independence, and yet retreat from their problems because of continued insecurity.

In seeking this new position they often deny the importance, continued dependency on, and authority of the parent. They thrive

From Letterman Army Hospital, San Francisco, Calif.

on praise. Directing this praise where it will do good, helping them to happy and successful experiences, and exhibiting trust—all contribute to the confidence they need.

The world of the adolescent is one of continual motion and competition. They live strenuously, work and play hard, compete against each other, and yet still have a very strong feeling of belonging with "the gang." A premium is placed upon physical appearance, clothes, complexion, and athletic and scholastic ability. The adolescent appreciates honesty and frankness and considers anything else a misuse of the trust they are willing to place in the physician.

A CLINICAL APPROACH TO ADOLESCENCE

The physician dealing with the adolescent is in an enviable position. He can offer the guidance, solid advice, and trust they seek. He is also able to provide a positive approach in clinical relationships. Adolescents prefer being told what they can do, not what they cannot do. The adolescent worried about obesity will take to a regimen that stresses what he can eat rather than to a series of dietary "don'ts."

Adolescents react more favorably to the physician and his advice when it is apparent they are responsible for their own care. They prefer to be able to state their own problems and dislike being brought into the office in the magnificent wake of one or both parents. The office should be free of toys and of the type of furniture that might give the impression that it is the office of a pediatrician. If the physician is to create a good impression, his own practice must be run in an orderly and punctual manner. Allowing adequate time for each patient is important. Neither party should appear or feel to be rushed. Initial conversation directed to sports, hobbies, and subjects other than medicine and school often foster friendship and serve to put the patient at ease.

If the visit has initially been requested by the parents who desire to state their views, such interviews are best accomplished on a day other than when the adolescent clinic meets. In essence, the adolescent should be allowed to seek his own medical care and not huddle in the shadow of the parent.

In a busy clinic or practice it is difficult to schedule appointments for adolescents during the day when it will not interfere with school. Evenings and Saturday mornings have become popular for this reason.

Adolescence as a time of life is without well-defined extremes. It may well run from age 12 to age 21. No age limit, therefore, may be set for patients seen in an adolescent clinic. Roughly trying to group the appointments by age serves to foster patient confidence. Our history taking should be both casual and complete. The importance of the menstrual history and the taking

of the blood pressure should be explained. Vaginal examination will be necessary only rarely, and when really necessary is best done under anesthesia. It is a psychologically traumatic experience at which less information may be gained (because of the tension it produces) than if a careful rectal examination had been done. Rectal examination also should be fully explained beforehand, both to avoid fright and to ensure better relaxation.

Because the adolescent is more willing to place his trust in one physician, referral to one consulting specialist after another is undesirable. A bewildering succession of visits to one physician after the other often raises doubt that any of them know what they are talking about, and dilutes the valuable patient-physician relationship. When consultation is necessary, the consultant, if possible, should come to the patient in the office of the clinic physician. This fosters the feeling that the adolescent and his physician are the important individuals concerned.

COMMON PROBLEMS OF THE ADOLESCENT

In successfully carrying out relationships with the adolescent the practitioner must at times assume the mantle of the pediatrician, dermatologist, orthopedist, gynecologist, internist, and psychiatrist. Some of the major causes for concern are discussed briefly below.

Growth. The radiological evaluation of bone age is often helpful in discussing this problem. If the bone age is normal the patient will usually either catch up with a growth spurt or slow down. The short, chubby adolescent is usually one who has not yet begun the adolescent growth spurt. An increase in leg length is often the first clue that such a period of growth is under way. In the absence of hypothyroidism and familial traits, growth will usually progress satisfactorily. An honest discussion about familial traits and the growth processes often is all that is required.

Obesity. If the patient can be acquainted with the relationship of prepuberal chubbiness and growth, and if organic disease can be ruled out, it is often possible to guide adolescents through this period without drug or dietary regimens. Overeating as an emotional outlet must be considered. If, after careful investigation, dietary control seems indicated, stress the foods to be encouraged and do not play up the don'ts of dieting. Make the diet appealing. Ensure adequate exercise and physical activity. Obesity and concern over a poor appearance go hand in hand. The determination of the patient may produce more gratifying results than the physician's counsel.

Sexual Maturation. Puberty and sexual maturation are often causes for concern. Early or late development of secondary sex characteristics, even though well within the normal range, may cause severe emotional disturbance, especially today when so

much emphasis is placed on anatomic evidence of sexual maturity. Reliable signs that all is progressing well are, in the female, budding breasts; in the male, penile changes; and in both, the axillary and pubic hair development and the changes in pigmentation associated with puberty. Frank discussion with the patient, stressing the variability of the time of onset of these changes, often has the desired effect in calming apprehension.

Acne. Even though acne is a relatively minor complaint to the physician, it is of importance to the patient because it deters from an otherwise perfect appearance. Acne has been responsible for withdrawal from school activity, decreased popularity socially, and scholastic failure because of the self-consciousness it engenders. Cleanliness and a good lotion are the basis of treatment. Mild dietary restriction may be indicated. It is well to remember that the adolescent patient with acne may well be using this as an entry for a more serious complaint.

Gynecomastia. Gynecomastia usually presents as a sometimes tender, button-shaped swelling under the areola. It is said to be experienced by approximately 80 per cent sometime during adolescence. A simple explanation that this is normal is usually all that is necessary. The other less common type results in a generalized enlargement of the affected tissue, giving the appearance of true breast enlargement. Here size is the chief concern, and it may be necessary to enlist the aid of the plastic surgeon.[5] Care should be taken to differentiate between Klinefelter's syndrome with its associated impotence.

Failure in School. School is to the adolescent what business or a profession is to the adult. It is his job. Apprehension over school work may be the underlying reason for psychosomatic complaints. This can often be ascertained through the simple expedient of studious listening and questioning during the visit. Standard writing and arithmetic tests should be a routine part of the work-up. A few students who have reading difficulty do reasonably well in school. Specific language defects and marked variance between chronologic and mental ages must be investigated.

Psychosomatic Complaints. Low back pain, headache, fatigue, precordial pain, or tachycardia may be the masked presentation of emotional stress at home, in school, or in relations with the patient's peers. Do not jump to the conclusion that the cause is organic, but do not label the disorder psychosomatic until the organic has been ruled out. The labile blood pressure of the adolescent (a pressure up to 140/90 mm Hg may be considered normal) may be responsible for a mistaken diagnosis of hypertension. Familiarity with blood pressure technics is important in avoiding the labile response, and is a good argument for the routine taking of blood pressures in pediatric practice.

Ulcerative Colitis. The responsibility of the physician is primarily that of offering advice, over-all guidance, and direction of the therapeutic program. Basic understanding of the patient is the cornerstone of the therapy. Diet, antibiotics, steroids, and surgery all seem to have an indicated role in therapy. The role of the emotions cannot be denied and must be carefully considered in evaluation of the patient.

Dysmenorrhea. A frank and practical discussion often pays dividends in helping young women with dysmenorrhea. Sometimes the philosophy of menstruation is learned solely from the mother who may give the impression that the physiologic process is meant to be painful, and dysmenorrhea is used as a means of obtaining sympathy. Is painful menstruation a feminine response to the tensions of adolescence? In differentiating primary from secondary dysmenorrhea, the administration of 1 mg of estrogen daily for 21 days, starting on the first day of the period, with a resulting pain-free period is good evidence that the difficulty is primary or nonorganic dysmenorrhea. Cramping may be normally associated with menstrual periods, or may herald the onset of ovulatory cycles. Menorrhagia, even though a physiologic alteration, is best discussed with the gynecologist. It is again emphasized that careful thought should be given before performing pelvic examination in the adolescent female.

A graphic record of the menstrual cycle is often helpful in understanding the physiologic nature of menstruation. Emotional evaluation is important. Does the onset of menstruation represent the end of childhood? Does the patient resent growing up? Would she rather be a boy?

DISCUSSION

It is becoming apparent the adolescent receiving his medical care in the service, together with many of his peers in civilian life, has no readily available source of sympathetic medical care. The peculiarities of nomadic service life often make serial follow-up difficult. To date, few adolescent outpatient clinics are in existence. Conversation with those pioneering the adolescent movement reveals that their experience came from actively working with the adolescent. Philosophies and technics were developed as a result of experience. A few actively interested service physicians could stimulate interest in adolescent medicine throughout the armed services. Careful consideration given to existing physical facilities usually will reveal an adequate plant for successful operation of an adolescent clinic.

The physician with a specialty may doubt the wisdom of working in the adolescent clinic with its atmosphere of "general practice," and the general-duty medical officer may express doubt in his ability to handle some of the specialized problems that occur. The relatively small number of patients seen is often

misunderstood as meaning that adolescent medicine is unrewarding. It is not volume of patients seen, but rather the standard of care given the individual that denotes the successful adolescent clinic.

Inasmuch as the average training program in both pediatrics and internal medicine currently makes no provision for training in adolescent medicine, joint operation of the clinic for adolescents would benefit the adolescent patient and provide excellent training for the resident physician.

Local interest has resulted in the formation of an adolescent clinic at this hospital. The clinic began operation in March of 1958, and has been incorporated into the teaching program of the pediatric service. It is thought to be the first such clinic in the armed services.

Communication on this subject between pediatricians in the service should be fostered, to stimulate interest in the adolescent. If present efforts result in the formation of a section for military pediatrics within the American Academy of Pediatrics, a fertile meeting ground for discussion will be provided. The problem of adolescence, and other mutual problems of pediatrics in the Armed Forces, would benefit.

SUMMARY

Adolescent medicine is a neglected field, and to meet the special problems and complaints of the adolescent there is need for the establishment of independently operating adolescent units in service hospitals. Co-operation between the pediatric and medical services could result in teaching material beneficial to both. An adolescent clinic is now in successful operation at this hospital.

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AN ECONOMICAL SUPPORT TO MAINTAIN A FUNCTIONAL FOOT POSITION IN BUCK'S EXTENSION

GEORGE E. OMER, Jr., *Major, MC, USA*
THOMAS J. ERWIN

GURDON BUCK[1] devised a skin traction system in 1857 that is an excellent appliance for relief of pain caused by muscular spasm or other conditions that require partial immobilization with simple traction for short periods of time. Buck's extension is applicable to a larger number of problems than any other one form of traction.

One technic for application of Buck's extension consists of placing the patient in a supine position with a firm mattress for support beneath the injured leg. The extremity is shaved and prepared by painting from knee to malleoli with benzoin or Ace Adherent.* Two strips of moleskin adhesive of suitable width are applied longitudinally to the inner and outer aspects of the extremity, extending from just below the knee to 8 inches beyond the sole of the foot. The moleskin strips are held in place by the Ace Adherent and an elastic bandage wrapped circularly from the knee to malleoli. An alternate method consists of placing thin strips of sponge rubber against the leg to prevent slipping, and over this the moleskin strips are compressed by 4-inch elastic bandages. After completing the leg, a 7½-inch canvas strap, 1 inch wide and with a buckle at each end, is tacked to a wooden block 2 inches wide by 4½ inches long, and with a ½-inch hole in the center. A traction rope is passed through the hole and over a pulley attached to the foot of the bed in a direct line with the affected limb. Weights of 5 to 10 pounds are added to the traction rope. The weight and pulley system is completed when the distal end of each moleskin strip on the leg is folded on itself to form a tongue which is adjusted and fastened into the canvas-strap buckle on each side of the wooden block.

The wooden block is wide enough across the foot to release pressure from the malleoli but does not have enough longitudinal

From Irwin Army Hospital, Fort Riley, Kans.

*Ace Adherent, manufactured by Becton, Dickinson & Co., Rutherford, N. J. (Federal Stock Number 6510-200-0160, Adhesive liquid, surgical.)

length along the sole of the foot to prevent plantar flexion contractures (fig. 1). In addition, a doughnut pad usually is required to relieve pressure on the heel against the firm bed. A prolonged

Figure 1. Buck's extension with and without positional support, demonstrating foot drop and heel pressure in apparatus without foot support.

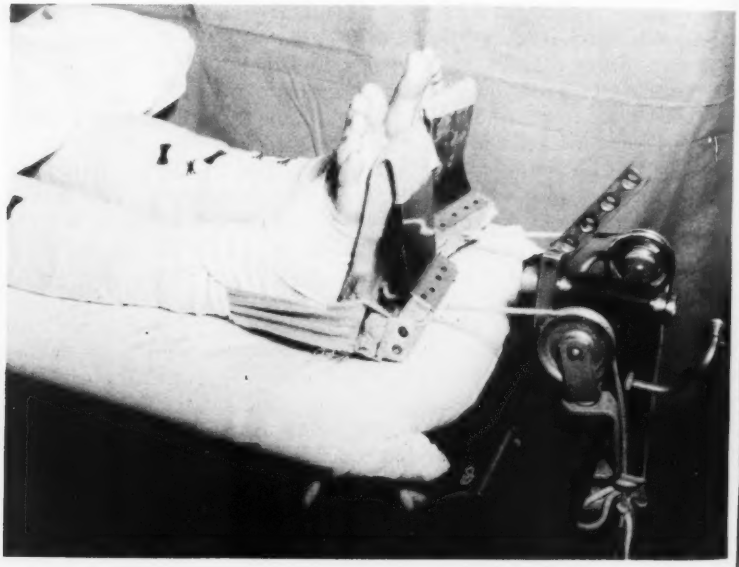

Figure 2. Buck's extension with aluminum foot support, demonstrating elevation of heel and 90° foot position.

positional foot drop can result and become a fixed deformity. The proper 90-degree functional position of the foot is maintained poorly with pillows or wooden blocks or even a sling over the foot pulling toward the patient's head.

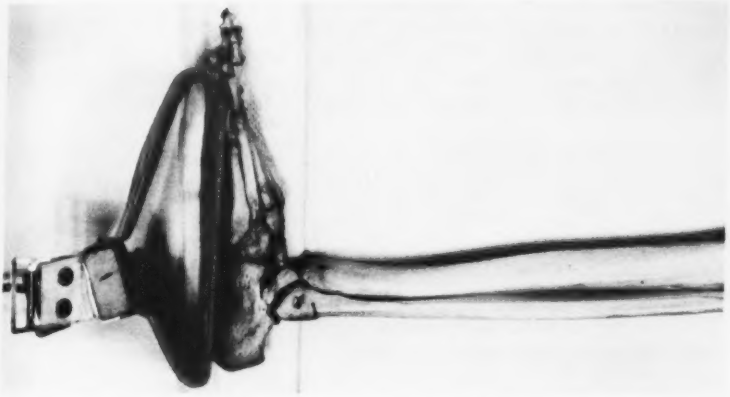

Figure 3. Brace showing relationship to bones in the foot and leg.

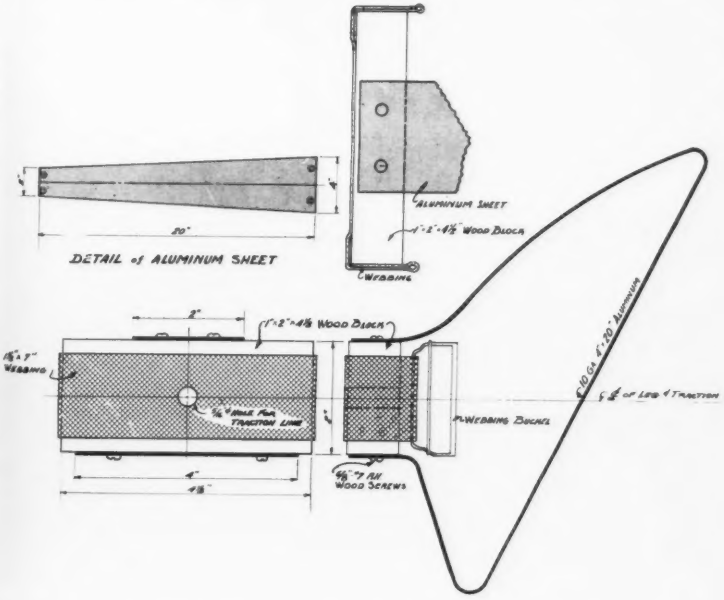

Figure 4. Working diagram for manufacturing brace.

To prevent foot drop and calcaneal ulcers during traction, a practical foot support is made from an aluminum metal strip, 4 inches wide and 20 inches in length. Of 10-gage weight, it is bent into a "C" shape, with the long flat edge against the patient's foot, and the two curved arms of the "C" fastened to the upper and lower sides of the wooden traction block (figs. 2, 3, and 4). The long curve of the "C" maintains the foot at 90°, and the lower end of the "C" elevates the heel from the bed and prevents cutaneous pressure lesions. Adhesive padding is used to cover the surface and edges exposed to the patient (fig. 5).

Figure 5. Buck's extension with aluminum foot support, showing adhesive padding of splint support and attachment of aluminum strip to wooden traction block.

The light aluminum material is easy to obtain, easy to cut, and costs approximately 15 cents for each foot support. It is strong enough to maintain the foot in functional position and can be used over and over again, simply by changing the adhesive padding against the patient's foot. It is believed that this is an economical and practical foot support to maintain a functional position during Buck's extension.

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MILITARY ASPECTS OF THE BIOLOGICAL EFFECTS OF RADIATION

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THIS report has been prepared to provide a review of the broad field of radiobiology as it applies to military problems.

There are some data available for man which are not particularly satisfactory. There also is a large volume of data obtained from laboratory and weapons test studies in experimental animals. It manifestly is not possible to cover within the scope of this document the entire field of radiobiology. This report attempts to review the problems; for details, it is suggested that the reader consult the general and specific references.

In many respects the physical weapons test data have been collected for the purpose of evaluating the hazard of ionizing radiation to personnel. Except at very high dosages (10,000 r and greater), ionizing radiation is without effect on ordinary material other than radiation dosimeters and photographic film. The basic purpose of this report is to provide some guidance in the use of physical data for the estimation of personnel hazard. In many, if not most, instances, the needed correlation between exposure dose and clinical findings is lacking because of insufficient data.

Source of Data. The primary sources of pertinent medical radiobiological information are:

1. The evaluation of the results of the Hiroshima and Nagasaki experience by the Atomic Bomb Casualty Commission.[1]
2. The evaluation of the results of the accidental exposure of the Marshallese during Operation CASTLE.[2]
3. Accidents in atomic energy laboratories.[3]
4. Clinical radiotherapeutic experience.

In addition, there is a large volume of experimental animal data from which certain inferences regarding man may be drawn, but which cannot be applied directly. In general, animal experiments indicate the pattern of response that may be anticipated

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in man, but are not an ideal source of information. Significant differences in details, particularly quantitative, preclude direct extrapolation to man. In fact, all sources lack certain pertinent critical information.

As an example, review of the problems associated with the calculation of radiation dosage at Hiroshima and Nagasaki result in the conclusion that at Hiroshima neutron effects might predominate while at Nagasaki, "nearly all the dosage is due to γ rays."[4] Aside from the difficulties associated with estimating the flux and energy spectrum of neutrons and the γ ray dose, there is considerable difficulty in assigning to a given location a number for dose because of the rapid decrease of the dose with ground distance, both for neutrons and γ rays. This is without consideration of an estimate of shielding factors. As will be discussed later, the biological effectiveness of neutrons may be greater than γ rays. Comparison of the results obtained at Hiroshima with those at Nagasaki should make some provision for this difference. But, in addition, the flux and spectrum for a given location are so poorly known that, in all probability, quantitative data purporting to relate lethality to dose are of dubious value.

The dosimetry problems associated with the exposure of the Marshallese make it difficult to determine precisely the γ ray dose.[2] The data were insufficient to permit even an attempt to be made to estimate the skin dose resulting from low-energy γ rays and β radiation. The many problems and uncertainties involved in the dosimetry of accidents in atomic energy laboratories are pointed out in a description of an accident at the Argonne National Laboratory.[3]

Types of Hazard. The personnel hazard may be divided into immediate and late considerations. The immediate hazard is that involved in the production of acute effects, principally lethality, acute radiation illness, or skin lesions. The long-term problem is that of the late effects; this involves both the individuals concerned and, through the genetic changes produced by radiation, their progeny for many generations.

Sources of Radiation. There are two separate sources of ionizing radiation to be considered. These are:

1. *External γ, β, and neutron radiation.* For residual radiation this is a combined β and γ radiation; for initial radiation, neutrons are an additional source of ionizing radiation.
2. *Internally deposited radioactive materials.* For military considerations, this is a problem associated with fallout.

EXTERNAL RADIATION

External radiation constitutes a potential hazard to personnel from the moment of detonation of an atomic weapon. The initial

radiation consists of γ and neutron radiation, propagated for large distances in air. In addition, within the cloud there is β radiation, but it is difficult to conceive of a situation where β radiation will constitute a personnel hazard before fallout occurs. While falling and after completion of fallout, the external radiation consists of both β and γ radiation.

Dosimetry. From the standpoint of estimation of personnel hazard from external radiation, the basic necessary physical data are:

1. The type of radiation, whether it be γ, β, neutron, or some combination of these.
2. Knowledge of the energy spectrum and flux.
3. Source geometry.

Units of Dose. There are several units of radiation dose currently employed.[5]

1. Roentgen—defined as the quantity of x or γ radiation that produces in 1 cm^3 of air at STP conditions 1 e. s. u. of charge of either sign.
2. Rep (roentgen equivalent physical)—that quantity of ionizing radiation which results in an absorbed dose in any material at the site of interest that is equivalent to that obtained from 1 r of x-rays; this quantity is usually taken as 84 ergs for 1 gram of air; for soft tissue this is 97 ergs/gm tissue. This unit is independent of the type or energy of the ionizing radiation.
3. Rad—that quantity of ionizing radiation which results in the transfer of 100 ergs/gm to any material. This is a recently adopted unit. It can be seen that for soft tissue it is almost equivalent to the rep.
4. Rem—roentgen equivalent mammal (man); to be defined later.

From these definitions it is seen that the roentgen is a unit applicable only to x or γ radiation, while the rep and rad are independent of the source type and energy.

Consideration of Depth-Dose Curve and Correlation with Biological Effect. The effect of ionizing radiation is dependent primarily upon the dose absorbed in tissue, *not* the dose measured in air. The basic problem is a determination or a calculation of the absorbed dose in tissue. This probably is best approached through the use of a depth-dose curve. A depth-dose curve is a graph of the relative amount of ionization produced at various depths in the body or some other absorber. Depth-dose curves have had extensive application in radiation therapy and in radiobiological research.[6] It is this experience that makes possible the quantitative prediction of biological effect from a depth-dose curve.

For the range of β particle energies encountered in fission products, maximum penetration into tissue is of the order of millimeters, while for x and γ rays and neutrons the degree of penetration can vary from a few mm to those which traverse the entire body. As a consequence of the change in absorption coefficient with x-ray energy, penetration into the body varies with the energy. For example, for 50 kvp x-rays the dose delivered to tissues deeper than 2 cm is small compared to that at the skin surface. The skin surface dose to produce an LD_{50} might reasonably be expected to be greater for 50 kvp x-rays than for 250 kvp x-rays, because the 50 kvp x-rays may be considered to produce a skin "burn," while with 250 kvp x-rays a relatively uniform dose throughout the body is produced. For dogs it has been shown that below 175 kvp the air exposure LD_{50} dose increases rapidly to 6,000 r at 50 kvp.[7]

The β particles arising from fission products constitute a source of radiation only for the skin and, in sufficient quantity, produce a condition known as a "beta burn" which can be lethal. The two principal considerations in the evaluation of the hazard of β radiation to the body are:

1. Dose to skin, and
2. Area of skin involved.

For example, it has been determined that the LD_{50}^{30}* for β radiation to the entire body varies from 1,500 rep (baby rat) to 30,000 rep (pigs); while the same dose range delivered to a small area of skin, *e. g.*, 1 cm^2, will not result in death, but will produce only local changes in the skin. The relatively low LD_{50} for β radiation for the baby rat is probably due to the fact that for such small animals there is significant ionization beneath the skin, and while this is not uniform total body irradiation, a considerably greater percentage of the tissues are irradiated than in larger animals.

The lethal dose for β radiation of man is not known.[8] Animal studies indicate that the total integrated dose to produce 50 per cent lethality may be directly proportional to the body mass. Extrapolation to man yields an LD_{50} for β radiation of approximately 40,000 rep, which is not in keeping with other data and should not be used for personnel-hazard calculations. On the other hand, from another line of approach, the β radiation LD_{50} dose is calculated to be approximately 5,000 rep. The latter appears to be a more acceptable value and is comparable to the LD_{50} for dogs for 50 kvp x-rays, but it is unestablished and must be considered only as an estimate of questionable value arrived at by extrapolation from animal data.

*Lethal dose for 50 per cent in 30 days.

X-rays and neutrons of sufficient energy produced ionization throughout the body resulting, when applied in sufficient quantities, in acute radiation illness.

Dosimetric Methods. In general, and for most peacetime applications, film badges are the most common dosimeters in current use. Varying sensitivity to various types of ionizing radiations precludes their use for precise dose measurements in mixed radiation fields. In addition, at weapons tests, where mixed radiations make the physical measurement of dose difficult, biological dosimeters have been used. Generally, mice are placed at various distances from the point of detonation in suitable containers to protect against the effects of thermal radiation and blast. Then the effects of the ionizing radiation are measured by one or more biological end points. The biological end points used are:[9]

1. Mortality (30 day).
2. Change in weight of the spleen and thymus.
3. Depression of red cell formation, as measured by the incorporation of radioactive iron into red cells.
4. Change in weight of the gastrointestinal tract.
5. Survival time (in the supralethal dose range).

The results then are compared with those obtained with x-rays in similar animals under laboratory conditions. The results are expressed not in terms of the mixed bomb ionizing radiation, but that at a particular station, the total effect of the ionizing radiations received is equivalent to a particular dose of x-rays.

Chemical and glass dosimeters also have been developed, but are less widely used.[5] It is possible that because of their relative simplicity, chemical dosimeters will become more widely used. Gamma radiation is generally best determined by some type of ionization chamber, although if suitably calibrated, photographic film may be used.

The measurement or calculation of neutron dose is more complex.[10] Fast neutrons are slowed down in tissue by elastic collisions, principally with hydrogen, resulting in recoil protons.

Capture reactions predominate with thermal neutrons; these are the n-p reaction with N^{14}, resulting in the emission of a 0.66 mev proton and the n-γ reaction with hydrogen, resulting in the emission of a 2.2 mev γ ray. Calculation of the dose at the surface and the depth-dose curve thus depends upon the flux and spectrum. Suitable ionization chambers in a phantom also have been used to determine the depth-dose curve.

Recently it has been observed that within the ground range of interest, the bomb neutron spectrum is relatively constant. Thus, a calculation of dose due to the entire bomb neutron spectrum can be carried out from the measurement of the flux of a single energy region.

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The dose due to β radiation is best determined by a suitable thin-walled ionization chamber. β radiation can be considered to arise from two sources:

a. β particles emitted from fission products upon the surface of the ground.

b. β particles emitted from fission products that contaminate the skin or clothing.

In the first case, the individual is in a field of β radiation, and, aside from consideration of the protection due to clothing and the attenuation of the flux with height from the ground surface, may be considered to be in a field of uniform β radiation. In the second case, however, there is in addition the β radiation arising from "hot particles" contaminating the skin or clothing and producing a local area of intense irradiation.

Directly measured depth-dose curves furnish the most satisfactory approach to the prediction of biological effect. The use of small ionization chambers in a phantom appears to be satisfactory. This type of measurement consists in the placing of small ionization chambers at various depths in a Masonite phantom. After exposure, the readings of the ionization chambers are plotted as a function of the depth from the surface of the phantom. This is a directly determined depth-dose curve for the particular source, source geometry, and receiver. For neutron irradiation a first collision dose calculation with an estimate of the attenuation due to depth is a good approximation.[11]

Significance of Air Dose, Skin Dose, and Mid-line Dose from X-ray Radiation[12]

Collimated beam-source geometry. Considerable confusion has arisen from failure to stipulate how the dose was measured. This is because from the same narrow collimated x-ray flux in air, these three quantities, air dose, skin dose, and mid-line dose, can and do differ significantly. Air exposure is the dose measured in free air, that is, without back scatter. Skin dose is the dose measured with back scatter, that is, the ionization chamber is placed at the surface of the body. Mid-line dose is the dose either measured in a phantom with size and radiation absorption characteristics similar to the biological object under consideration or calculated from a knowledge of the energy spectrum and absorption constants. The skin dose is higher than the air exposure dose due to back scatter. The mid-line dose is a function of the energy spectrum and body size and is usually less than the air dose and skin dose.

The relationship between air dose and mid-line dose is dependent upon the source and receiver geometry and with low energy x-rays on the absorption constant. Because there is considerable variation with energy in the absorption constant,

the ratio air dose/mid-line dose can vary considerably. For example, from weak x-rays (below 50 kvp), the mid-line dose may be negligible as compared to the skin dose, in which case the ratio mid-line/air dose will be very low while in the γ ray region this ratio may approach 1. It can be seen readily how failure to stipulate the measurement conditions may lead to considerable confusion.

Infinite plane-source geometry. For the case of radiation in a fallout field, *i. e.*, infinite plane-source geometry, the relationship between air dose, skin dose, and mid-line dose is different. Direct observation of the hard γ radiation component of a fallout field in a phantom Masonite man indicates that within the error of measurement there is no appreciable change below 3 cm with depth, that is, the γ radiation depth-dose curve is relatively flat, and equal to the free air exposure in roentgens, as measured by a thick-wall ionization chamber.[2]

Which of these three measurements, air, skin, or mid-line dose, is the most satisfactory? In all probability, there is no single measurement which will be satisfactory in all cases. For weak x-rays (below 50 kvp) certainly the mid-line dose is unsatisfactory, while the skin dose or air dose may be misleading if it is not realized that this radiation is essentially body surface or skin radiation. The measurement to be used depends upon the biological end point under consideration. The mid-line dose is to be used when total body irradiation, acute radiation illness, and lethality are under consideration, as it affords the best correlation between dose and effect. However, for consideration of the skin beta "burn" hazard, it is necessary to know the dose to the skin. It thus is apparent that a single measurement or calculation is not satisfactory for all cases. For military operational purposes, it has not been determined if it is necessary to know both the skin and mid-line dose.

For the fallout field where there is a combination of both β radiation and weak x-rays and γ rays, the use of the phantom Masonite man probably defines the problem most satisfactorily, because the results permit an evaluation of (1) the dose to skin and (2) the whole body dose. The results may be expressed as a ratio $\left(\frac{\beta}{\gamma}\right.$ dose ratio$)$.[2] Experimentally this measurement has been carried out in a limited number of conditions. Values of the $\frac{\beta}{\gamma}$ dose ratio varying between 2.5 and 28 have been observed at field tests.[13] Dale has worked out on a theoretical basis the variation with time of this ratio, up to 400 days. Initially, the ratio of surface dose to mid-line dose is high, approximately 15 or 20, decreasing to a minimum of about 2 at 10 to 20 days.[13]

CONCEPT OF RBE (RELATIVE BIOLOGICAL EFFECTIVENESS)[14]

With the availability of various types of ionizing radiation, it early became apparent that prediction of the effects of a given physical dose was inaccurate when the biological effects of heavy ionizing particles were compared to those of x-rays. This was particularly true for external neutron irradiation. Initially, neutron doses were measured with a Victoreen ionization chamber and in units of n. One n is the neutron flux to produce a reading equivalent to 1 r in a 100-cm^2 Victoreen ionization chamber. Recently it has been confirmed that 1 n $\cong$ 2 rep.[15] The biological effect of 1 rep of neutrons is greater than would be anticipated from 1 rep of γ radiation, and to rationalize this discrepancy, the concept of relative biological effectiveness (RBE) was introduced. When compared to x-rays, and for equivalent biological effect, the flux required of any ionizing radiation is the product of the RBE and the dose delivered in rep unit flux. It should not be inferred that RBE is used only in connection with neutrons. The RBE has been determined for α particles, protons, and β particles, and within the spectrum of x and γ rays.[16]

RBE is not a simple concept, it depends upon:

a. Type and energy spectrum of ionizing radiation.
b. Biological end point measured.
c. Dose and dose rate.[9]

It is particularly when different biological end points are considered that a large range of values for RBE are encountered. With the development of the concept of RBE, a new unit, the rem (roentgen equivalent mammal (man)), came into use. The rem is the product of the absorbed dose (in rep) and the RBE for the particular type of ionizing radiation used and biological end point measured.

An explanation for the fact that from a given physical dose, the magnitude of the biological results varies probably is related to differences in linear energy transfer.[14] Basically, it has been observed that, for the same physical dose, as the linear energy transfer (or the density of ionization per unit path length) increases, the magnitude of the biological effect goes through a maximum. A rigorous discussion of the mechanisms involved is not attempted here. Then for the heavy charged particles (α particles and protons), the biological effect generally will be greater than for γ rays. Because most of the energy transmitted to tissues from neutrons is through the ionization produced by recoil protons, it would be anticipated that, for a given physical dose (ergs/gm), neutrons would produce a greater biological effect than γ rays. For military medical purposes, an important RBE, but not the only one desired, is the RBE for bomb neutrons for acute lethality. Field tests indicate that this particular RBE is approximately 1.7 in mice.[17] For

60-inch cyclotron fast neutrons with a different spectrum, this RBE in dogs is approximately 1.0.[18] This indicates that the estimate of 1.7 may be high, and that the RBE for acute lethality for man for bomb neutrons may be 1.0 or less.

DESCRIPTION OF ACUTE RADIATION SICKNESS

Symptomatology. For military medical purposes, the acute radiation syndrome should be considered from the following standpoints:

1. Symptomatology and relationship of symptomatology to continued military effectiveness.
2. Incidence and duration of symptoms as a function of dose.
3. Incidence of lethality as a function of dose.

For man the most useful sources of information are (1) the evaluation by the Atomic Bomb Casualty Commission (ABCC) of the Hiroshima and Nagasaki experiences,[1] (2) experience derived from clinical radiation therapy,[19, 20] and (3) the evaluation of the Marshallese exposed in March 1954.[2] Unfortunately, all these sources of information contain basic uncertainties precluding good quantitative conclusions.

The Hiroshima and Nagasaki data are valuable for a description of disease, but cannot be correlated closely with dose because the dose is not known nor are estimates of the dose good. The clinical radiation therapy experience is complicated because most is partial body radiation; in addition, it is complicated seriously by the underlying disease for which the patient is receiving therapy. Furthermore, many patients have imparted to them some degree of awareness of nausea and vomiting as possible complications of radiation therapy, making this symptom difficult to evaluate. The knowledge gained from the study and treatment of the Marshallese also is complicated by uncertainty as to the dose received and the effect of a changing dose rate.

The situation is such that for the acute radiation syndrome, the symptoms encountered can be described, but evaluation in relation to dose, more importantly quantitative evaluation as to incidence, particularly in the range from no symptoms to 50 to 60 per cent of individuals symptomatically affected, is not available. There also is no information available for the case of protracted radiation, other than that obtained from the accidental exposure of the Marshallese.

The earliest symptoms are nausea and vomiting, generally occurring within 6 hours after a single, acute, whole-body, penetrating γ ray exposure. Hereafter in the discussion, it is implied that the air-dose figure mentioned does not include

scattered soft γ radiation. The incidence of nausea and vomiting as a function of dose is not well known. Probably, below 50 to 100 r (air exposure), there are no symptoms, and above 250 r to 300 r there is 100 per cent involvement, but between no involvement and 100 per cent involvement the data are meager.

The sickness dose for 50 per cent of the population exposed is estimated as 150 r. In a study of a small group (about 20 patients) treated with 200 r (skin dose) unilateral, almost whole-body radiation exposure, nausea and vomiting was noted in approximately 30 per cent.[19] In a second study of 30 patients exposed to a total air dose of 200 r, with 100 r delivered to each side of the body, 27 patients (90 per cent) were symptomatic.[20] In 17 patients, the reaction to radiation included vomiting. Of the Marshallese exposed to 175 r (air dose) over a period of approximately 46 hours, with 75 per cent of the dose delivered in 36 hours, nausea was noted in two thirds and vomiting and diarrhea in 10 per cent. At doses below 200 r there are no additional symptoms.

When both nausea and vomiting exist, it should be presumed that such individuals are not capable of satisfactorily performing a military task. There is no information on the capability of man to perform work following an exposure to radiation sufficient to induce these symptoms, nor is there adequate information as to the duration of these symptoms. Other clinical states involving nausea, vomiting, and diarrhea generally are associated with malaise and lassitude sufficient to prevent the carrying out of useful physical work. In addition, the unevaluated and unknown degree to which individuals are motivated may play an important role. For the present, the assumption of inability to perform a task probably is the best that can be made. The time required for recovery from these symptoms to full working or even partial working capability is not known, possibly a few days are sufficient.

At higher dose levels, additional manifestations of radiation sickness appear, generally after a latent period of a few days. Because of the scarcity of data, it is difficult to describe the precise time-course of the onset and extent of involvement, although various tables have been prepared, in general having their origin in the Hiroshima and Nagasaki experiences.

Following the initial nausea and vomiting, there is a latent or asymptomatic period varying from 1 to 3 weeks at 200 r to perhaps of the order of 1 week in the mid-lethal range (400 to 500 r). Following the asymptomatic period, at 2 to 4 weeks after exposure, malaise and loss of hair (epilation) occur and small hemorrhages (petechiae) appear in the skin and mouth. Ulcerations occur in the mouth, with symptoms similar to those of a sore throat, plus bleeding from the gums. Similar ulcerations

in the bowel result in diarrhea. These complications are associated with alterations in the blood-clotting mechanisms and a leukopenia. In the more heavily exposed (within the lethal range), anorexia, weight loss, and fever become the prominent symptoms. The red blood count decreases and the symptoms become more pronounced, leading to death. Analysis of the Japanese experience indicates that percentage lethality can be correlated with lowest white blood count at particular times. In the survivors, there is a variable period during which recovery takes place. In the range of moderate to marked symptomatology, recovery to the point of being able to perform usual tasks may be of the order of 3 to 6 months or even longer.

At supra-lethal doses, 1,500 r or greater, central nervous system alterations have been observed in monkeys.[21] At very high doses (10,000 r or greater) delivered in less than an hour, death may supervene during the irradiation or within a few hours. In monkeys, lethargy, convulsions, and other neurologic manifestations occur. No data are available for man in this dose range.

At present it is not possible to predict for a given air dose for either unilateral exposure or for infinite plane source geometry the percentage lethality. It is recognized that for unprotected exposure in a fallout field, there is received a combined β and γ radiation. Consideration of the biological effect of this type of mixed radiation is not possible at present. Probably, below 200 r air dose there will be no lethality, or at most, a few per cent, while above 700 r there will be few survivors.

Where in this range the LD_{50} falls is open to question. By convention it has been set at 400 to 450 r (with an unspecified source and source geometry), but this is not fixed. Furthermore, the shape of the mortality versus dose curve is not known for man. In experimental animals, this shape has been determined in a large number of experiments. A convenient method of expressing the result is the probit transformation, as this transformation results in a straight line. It must be pointed out, however, that these studies in animals, except for a few such as those carried out in mongrel dogs, have been conducted with pure-bred laboratory animals of the same age. To postulate similar results from a probit transformation in man is not reasonable. In addition, the effect of changing the source geometry is not known for man, although it would be expected that a change from unilateral to bilateral exposure or to infinite plane-source geometry would produce a significant decrease in air LD_{50} dose, as it does in the pig.[22] The original analyses of the Hiroshima and Nagasaki data and speculation lead to the adoption of 450 r as an LD_{50}. The experience gained from the Marshallese suggests a lowering below 450 r.

It should not be thought that these indicate basic differences; the original figures derived from the Japanese data are subject to considerable error with regard to dose, and are for unilateral, single, short duration radiation; while the Marshallese data result from a more protracted radiation, with an infinite plane-source geometry plus an unknown quantity and unknown effect of β radiation to the skin, and from the opinion that the dose received was on the borderline of lethality (50 to 100 r more would produce some mortality). Recent review of the Japanese data in the light of newer weapons-test data suggests an increase of the LD_{50} to approximately 650 r (air dose).

Current Therapeutic Concepts.[23] As a basis for discussion, it must be presumed that at present there is no specific curative treatment for the acute radiation syndrome in man. For the experimental animal, there are a number of modalities used either before or after irradiation, leading to reduction in acute mortality. These are (1) radiation in the hypoxic state, (2) transfusion of bone marrow or spleen or homogenates of bone marrow or spleen, (3) various chemicals, *e. g.*, cysteine, (4) antibiotics, and (5) blood transfusions. Only the last two are, at present, to be considered applicable to man.

In clinical radiation therapy, amelioration or reduction in the incidence of nausea and vomiting has been claimed for a number of diverse agents, *e. g.*, (1) adrenocortical hormones, (2) adrenocorticotrophic hormone, (3) various vitamin preparations, and (4) β-mercaptoethylamine. All of these are of somewhat dubious value. Lacking a specific therapeutic agent or regime, treatment has been asymptomatic and supportive. Bed rest, fluids, antibiotics, and transfusions have been used as indicated.

Problem of Partial Body Shielding. Clinical radiation therapy experience and extensive experimental animal research indicate that shielding part of the body is effective in reducing the magnitude of the acute radiation injury and is associated with an accelerated recovery, particularly of the bone marrow. It is probably this latter fact that accounts for the reduction in mortality. The value of such shielding in military situations is difficult to estimate. The degree to which this permits an individual to raise head and shoulders above ground level while in a foxhole or be exposed through an aperture in some other shielding and avoid the consequences of radiation injury is not known. An additional problem in shielding considerations is the fact that the more desirable types of shielding for neutrons are not the same as for γ rays.

Description of Beta Burn.[3] For localized β radiation, the best clinical description available is that of the results in the Marshallese. In these individuals the minimum time for development of skin lesions was 12 to 15 days. The first indication

of the development of a skin lesion was an increase in skin pigment in localized areas. This was followed by scaly desquamation in the central portion of the lesion, leaving an area of pink depigmented skin. Gradually the pink area spread out into the darker-pigmented area, with eventual complete healing. In other areas, presumably where the dose to the skin was greater, blisters developed. These opened, leaving a raw, weeping area. This is comparable to a second degree thermal burn. New skin covered these areas in 7 to 10 days, and was followed by pigmentation.

Unfortunately, the dose to the skin could not be measured and cannot be calculated or estimated, other than by comparison with the effects of x-radiation given in single or multiple doses. Presumably, lesions that developed blisters resulted from a dose to the skin, which, if the total body skin were involved, would be lethal. However, if lethality is comparable to that observed in thermal burns, involvement of less than 100 per cent of the skin would result in lethality. For example, an untreated 33 per cent body-surface area, second degree, thermal burn is in the lethal range. Probably similar results would be obtained with β radiation. Except for S^{35}, the surface dose required to produce recognizable epidermal injury for pigs, sheep, rabbits, rats, and mice is from 1,500 to 5,000 rep. For S^{35} it is 20,000 to 30,000 rep.[2] Higher doses are needed when S^{35} and other weak β emitters are used, as only a small fraction of the β particles will penetrate to the sensitive layer of the skin.

LONG-TERM (LATE) EFFECTS

Shortening of Life Span.[24] The long-term effects of irradiation can best be considered from the standpoint of reduction in life span. Animal experimental data clearly indicate that one of the consequences of total body x-radiation in sufficient quantity is shortening of life span. This reduction in life span is conspicuous in the case of those who develop leukemia, but other tumors also may have their origin in radiation. In many instances, however, there is no specific pathologic change attributable to x-radiation except for a general pattern of premature aging. For this reason, shortening of life span, which represents the end result of all the injury produced, is probably the most sensitive and satisfactory criterion for determination of the long-term hazard.

There are several different mathematical approaches to the study of this problem. These are the adaptation of the Gompertz formulation to radiation, the Sacher and the Blair theories. From the available animal data, the life-span shortening in young animals for a single acute dose is on the average 3 per cent per 100 r. The relationship between reduction in remaining life span and dose is linear. For older animals, theory predicts

that the percentage reduction of life span increases approximately threefold.

What can be said about man? At present, there is only one suitable opportunity for observation and that is the experience at Hiroshima and Nagasaki. It is possible, but not probable, that some data regarding shortening of life span from a sublethal dose of radiation may become available from the continuing study of the Marshallese. However, it has been reported that radiologists have an average life span of 5.2 years (approximately 12 per cent) less than other physicians not exposed to radiation. This reduction is compatible with the extrapolation of the animal results to man, and estimates of the exposure of radiologists to radiation. Brues and Sacher[25] have developed two postulates for the extrapolation from species to species. These are:

1. For the single acute dose—the percentage reduction in life span is the same.

2. For chronic irradiation—to produce the same percentage reduction in remaining life span, the dose rate should be Y, where

$$Y = \frac{\text{life span species 1}}{\text{life span species 2}}$$

Thus, for man, the dose rate to produce the same percentage decrease in life span should be approximately one eighteenth that observed in the rodent.

There are two features of Blair's theory and method of analysis that require further explanation. The Blair theory predicts that the acute-dose LD_{50} decreases with age, and that this decrease is linear. This has been tested in only a very limited way, and indeed the acute-dose LD_{50} does decrease with age in rats, but the data are not sufficient to determine the rate of decrease of LD_{50} with age.[26] Because of certain pulmonary complications observed in older rats, extension of this observation to other species may not be warranted. The Gompertz-function type of analysis also predicts that the LD_{50} should decrease with age. Since aging and irradiation injury are additive, older animals will require less additional injury, whatever the source, to produce death, if the injury produced is comparable to normal aging. For man, there is no information available on this aspect.

Cataracts. The dose to produce cataracts in man is not known with any degree of certainty. It probably is relatively low for x-rays, in the range of LD_{50}, and considerably lower for neutrons. Cataracts are a particularly serious potential complication of neutron radiation. The RBE for cataract formation from neutrons is approximately 10 to 20.

Fertility. This is difficult to evaluate quantitatively. Depending upon the dose, there can be anything from a mild depression of sperm formation up to permanent sterilization. The dose for permanent sterilization is slightly higher than the lethal dose. In males a single sublethal dose results in a decrease in sperm count; this can be considered as relative sterility. Recovery is a slow process, taking up to one year. For the female, doses of 125 to 150 r produce amenorrhea, and 170 r produces sterility of 12 to 36 months duration. Parenthetically, it is of interest to note that survivors of serious radiation accidents have produced children.

GENETIC EFFECTS

That radiation results in genetic changes is unquestioned. While much work has been done on the genetic changes induced in lower organisms, particularly the fruit fly, there are few mammalian experimental data and those almost entirely in the mouse. The great uncertainty for man is the relationship between dose and number of mutations produced and their manner of expression. In general, it is assumed that radiation-induced mutations are deleterious. Genetic changes would be a problem for the survival of mankind if the whole population or a large fraction of the population were to be heavily exposed; radiation of small groups is more a problem in the concern of the individual for the welfare of his progeny than for the survival of mankind, but cannot be neglected. With the increasing development and use of various radioactive isotopes for nonmedical purposes and the use of reactors for propulsion and power systems, large numbers of people may be exposed to radiation. Thus, the small groups may become considerably larger in the near future.

There are several observations regarding the genetic changes induced by radiation that may be summarized as follows:

1. Most, if not all, radiation-induced mutations are deleterious.
2. There is no recovery from radiation-induced genetic changes.
3. The amount of injury produced is directly proportional to the total dose.

From experimental observations in fruit flies and mice, it is suggested that a dose of 30 to 80 r to the entire population would double the mutation rate. The consequences of this are difficult to estimate, because the manner of expression of many of these genetic changes is not completely understood; in fact, it is but little understood. These changes could find expression in terms of various constitutional deficiencies, varying from those that result in a shortening of life span to those involving

the capacity to perform mental tasks. It is entirely possible that doubling the mutation rate could be a serious burden, economically and medically. It has been recommended that the average dose for the reproductive period be kept below 10 r above background.[27] For some individuals this may be exceeded, but should be limited to a total dose of 100 r, of which no more than 50 r should be accumulated before age 30.

EFFECT OF PROTRACTION AND FRACTIONATION

Both evidence from animal experiments and experience with clinical radiation therapy clearly indicate that protraction of the delivery of the dose for days, weeks, or months, or fractionation of the dose over similar periods of time, results in a smaller biological effect (generally a lower incidence of lethality) than does a single dose of the same magnitude delivered over a period of minutes.[24] This does not include genetic effects.

This implies recovery from the injury produced by radiation. The rate of recovery may be measured by administering a sublethal dose, generally one half LD_{50}, and then at various later time intervals determining the additional dose required to produce 50 per cent lethality. Such experiments show that the amount of the second dose to produce 50 per cent lethality increases with time. However, experimental studies show that recovery is not complete; the irreparable component amounts to about 10 to 20 per cent of the injury produced.

In the mouse, the recovery rate is from 10 to 20 per cent/day; in the rat, 7 to 10 per cent/day; in the dog, about 4 to 5 per cent/day; and in the monkey, 14 per cent/day.[24] The recovery rate for man is not known. Studies of the recovery rate for erythema (reddening of the skin) in man indicate much larger recovery rates; however, this is not the recovery rate desired for military medical purposes. Actually, the recovery measured in lethality experiments is not a single physiologic process; it represents the net recovery of all the physiologic processes necessary for the maintenance of life, with each weighted according to its significance in the maintenance of life.

The effective dose is defined in terms of the results of a single acute dose, and is best illustrated by an example. If the acute dose to produce 50 per cent lethality within 30 days is 400 r, then the effective dose of any system of fractionation or protraction that produces 50 per cent mortality in 30 days is 400 r, although the physical dose may be much greater.

From the Blair theory, for the particular case that the animals are young, that each dose is administered within a short period of time, and that death occurs in a few weeks

$$D_{eff} = \left[(nf) + (1 - f)\ \frac{(e^{n\beta t_2} - 1)}{(e^{\beta t_2} - 1)}\right] \Delta$$

where f = fraction of injury, irreparable
Δ = dose
n = number of doses
β = rate of recovery
t_2 = interval between doses (days)

For man it is recommended that $\beta = 0.05$ day^{-1} be used. It also is recommended that a value of f between 0.10 and 0.20 be used, although there is no evidence to support this recommendation. Other relationships have been proposed for calculation of the effective dose, but they are not satisfactory.

INTERNALLY DEPOSITED MATERIALS

Source. The radioactive isotopes produced in the process of fissioning of uranium and plutonium in an atomic explosion are distributed widely over the entire world by the winds. There is a slow settling of these particles from the atmosphere, the rate of descent being governed by particle size and shape, and the location of the fallout being dependent upon the rate of descent and wind patterns. There are a number of variables involved, none of which is completely understood. A particularly valuable source of information and summary of the current status of the fallout problem is to be found in the hearings of the Joint Committee on Atomic Energy.[28] The quantity of material in the stratosphere and the rate of movement from the stratosphere to the troposphere have been estimated, the latter having an average residence time of approximately 10 years and the former having been estimated as varying from a few per cent to over 50 per cent for a land burst.

Route of Entry into Man of Fallout Fission Products. There are three routes of entry:

1. Inhalation
2. Ingestion
3. Open wounds.

Inhalation. During the period when radioactive particles are falling out, inhalation is a route of entry into the body. After settling on the ground, these particles can become airborne again and thus available for inhalation. The distribution within the respiratory passage of radioactive particles inhaled is dependent strongly upon particle size. In general:

a. Particles less than 0.1 μ are inhaled and then exhaled.
b. Particles 0.1 μ to 3.0 μ reach the lungs and are deposited in the alveoli.

c. From 3.0 μ to 10 μ, particles reach and deposit themselves upon the walls of the trachea, bronchi, and bronchioles, then work up to the larynx and ultimately are swallowed.

d. Above 10 μ, particles are filtered out in the nose.

Rainfall occurring at the time of passage of the atomic cloud has been shown to result in an increase in the urinary cesium^{137} and I^{131} content of man, strongly implicating inhalation as a significant route of entry.[28]

Ingestion. Radioactive materials settling on the ground may be incorporated into or coat the surface of plants that subsequently are eaten by man or by livestock which later are eaten by man. Evaluation of the importance of this route of entry and the hazard involved is complex. Movement of fission products through the soil, uptake by plants, use of plants for animal fodder, and subsequent ingestion by man, all are important and only partially documented factors. The presence and amount of strontium^{90} in man is well documented, although the details, particularly quantitative, of the movement of this Sr^{90} through the biosphere are lacking.

The relative significance of these two routes of entry is still to be determined. Water does not appear to be a significant route of entry of fission products into man. However, this may not be applicable for local fallout.

Open wounds. Open wounds do not appear to be a significant route of entry into man, except in unusual circumstances.

Metabolic Fate. The metabolic fate of the fission products is dependent on a number of factors. For each element it is different, and for each chemical species of a given element it may be different. For example, particles inhaled and reaching the alveoli, if they are soluble in body fluids, are absorbed, reach the blood stream, and subsequently are distributed throughout the body in accordance with the manner in which the body treats that particular compound. If insoluble, the particles may be concentrated in the lymphatic system of the lung and remain within the lungs and associated lymph nodes for that individual's lifetime, constituting local areas of intense radiation. These considerations of particle size and chemistry must be applied to all of the fission products.

Within the gastrointestinal tract, similar considerations apply. For materials that are absorbed, the distribution in the body varies. For example, iodine, as iodide, is taken up by the thyroid gland and subsequently released to the blood stream as organically bound iodine.

Probably most important is the fact that many of the fission products that reach the blood stream are taken up and retained for long periods of time by bone. Animal experimentation and

the history of radium-dial workers indicate that this may lead to serious complications, such as malignant bone tumors, although other less serious pathologic conditions can and do occur. In fact, in animal experiments it can be shown that such bone deposition can lead to shortening of the life span even in the absence of specific pathologic changes in the bone.[29]

Biological Effects. The quantities of most materials that can gain entry into the body are such that if a material is not a normal metabolite, the quantity present is not sufficient to be toxic merely by virtue of its chemistry; the injury produced is that of irradiation of the tissues. Depending on the tissue involved, the dose, and the dose rate, a wide range of pathologic changes may occur. These will vary from no discernible anatomical change, but with subtle physiologic changes for low doses, to the production of malignant tumors at higher doses. The latent period for these changes may, as in the case of radium-dial workers, be up to 10 to 20 years or more.

Therapeutic Aspects. The therapeutic problem is largely concerned with a particular class of isotopes; namely, those associated with deposition in the bone and commonly called "bone seekers." Unfortunately, therapeutic measures now under investigation, principally removal by chemical agents, are not particularly promising.[30] Therapy of the radiation injury produced by internally deposited radioactive isotopes is as unsatisfactory as for external radiation; there is no good means of treatment.

Analysis of the biological properties of the fission products has indicated that the long-lived isotope of strontium, Sr^{90}, is the greatest hazard, although it is not the only long-lived isotope that may be hazardous. Project SUNSHINE has reviewed the biological properties of strontium, the world-wide distribution, in particular in food and water, and the present levels of body burden of Sr^{90}.[28] The fact is that Sr^{90} is now present in human bone and is thought to be derived from food, principally dairy products. At present the quantity of Sr^{90} present in man is low compared to estimated toxic levels. The change in bone Sr^{90}-content with time is partially known; but a good evaluation of the tolerance level is lacking. Recent work implicates an inhalation route of entry as at least partially responsible for the present body burden. While considerable attention has been directed towards Sr^{90}, other fission products can and do gain entrance to the body. It is the bone deposition of Sr^{90} that gives rise to concern; the majority of the other fission products are either produced in small quantities compared to strontium, are relatively rapidly excreted, or have short physical half lives. In the latter class fall the iodine isotopes. Nevertheless, they contribute to the injury produced and should not be ignored.

COMBINED INJURIES

Experiments with swine, dogs, and rats indicate that the lethality of combined nuclear-radiation damage and thermal injury is greater than would be expected. [31, 32] These studies have been carried out by determining the mortality produced by thermal injury alone, by radiation injury alone, and by combined injuries. For example, thermal burns and radiation exposures that, by themselves, would result in no mortality give rise to significant mortality when combined. Also thermal burns or radiation injury at levels that alone result in low mortality, may when combined lead to considerably greater mortality than expected. Quantitative translation of this data to man is not possible at this time. Nevertheless, it should be anticipated that in man the same findings will occur, namely, that these effects are not simply additive. It also is probable that similar results will be obtained when radiation is combined with other forms of traumatic injury. A calculation of the magnitude of this effect is not possible, and the variety of types of traumatic injury is such that any calculation would be of little value.

MAXIMUM PERMISSIBLE LEVELS OF RADIATION

As a fundamental premise, it must be considered that all radiation is deleterious. However, radiation and certain radioisotopes have come to play important roles. For example, great strides have been made in medicine since the introduction of the x-ray for diagnostic purposes; radioactive isotopes have proved to be a potent tool in medical research and to have therapeutic value in certain diseases; the industrial uses of x-rays and radioactive isotopes are increasing rapidly; and finally, reactors are being used for the production of power. With all these beneficial uses, there comes the hazard involved.

External Radiation. Since the introduction of x-rays, as more data on the late effects of irradiation became available, there has been a progressive reduction in what has been considered to be a "safe" maximum level of exposure. Handbook No. 59, National Bureau of Standards, reviews the present "tolerance" levels. In general, it is recommended that for continuous total body x or γ radiation, the maximum permissible exposure be 300 mr/week.

Internal Radiation. The maximum allowable concentration of radioactive isotopes in the body is based largely upon the assumption that the dose rate to the critical organ be no greater than 300 mr/week. Because of varying biological properties, the critical organs vary with different isotopes. In general, bone and bone marrow are the critical organs, although not for all isotopes. Handbook No. 52, National Bureau of Standards, lists values of the maximum permissible amount for a number

of isotopes. Calculation of these quantities is complex, and depends upon the distribution within the body, the radiations emitted, the biological turnover time, and for γ emitters an estimate of RBE or comparison with radium. There are many uncertainties involved, and like the limits set for external radiation, those for internal radiation are being reviewed.

Recently an additional restriction limits the exposure rate for both external radiation and internal emitters to individuals in controlled areas, *i. e.*, those occupationally exposed, and in addition limits the dose according to the formula,[33] MPD = 5 (N-18) rem, where N = age in years and MPD = maximum permissible accumulated dose.

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TOXICOLOGY AT THE ARMY AREA LABORATORY

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AN ever-increasing demand for the identification of toxic substances in biological specimens has become evident in recent years. A review of this subject, together with a discussion of the submission of specimens, may serve to answer a number of questions and to clarify some of the problems encountered.

As stated in Army Regulation 40-440, "Toxicologic studies, virus and rickettsial procedures, and studies in connection with medicolegal and epidemiologic problems will be carried out to the extent that trained personnel permits."[1] It therefore becomes the duty of the Army Area Laboratory to carry out toxicologic investigations for all of its submitting agencies, which may, on a regional basis, include certain Navy and Air Force facilities.

The term, toxicology, as used in this laboratory, means the identification of foreign substances in biological fluids and tissues. No evaluation of the toxicity of these substances is made, such as determination of minimal lethal dose (MLD) or median lethal dose (LD_{50}). Instead, the problems studied are use of narcotics, coma possibly caused by sedatives (barbiturates), and accidental or intentional poisoning by a great variety of agents. It is this laboratory's function to identify and attempt to quantitate such substances.

SUBMISSION OF SPECIMENS

One of the most basic problems with which we are faced is the submission of specimens.

Choice of Specimen, Quantity, and Packaging

There are several excellent references[2-4] concerning the choice of specimen as related to the suspected substance, and each person submitting specimens should familiarize himself with this information. Table 1 is a partial listing of the type of test desired and most desirable specimen to submit, together with the quantity that should be submitted. In autopsy cases, however, one should submit as many different specimens as considered

From Sixth U. S. Army Area Medical Laboratory, Fort Baker, Calif.

necessary to determine the causative agent. Along with biological specimens, physical evidence, such as syringes, tablets, powders, and other objects that might be implicated, should be obtained and submitted.

TABLE 1. *Choice of specimen and minimum quantity for tests for various poisons suspected*

Poison suspected	Specimen best suited	Quantity
Alcohol	Blood; brain	50 ml; 500 grams
Alkaloids	Urine	All available
Antihistamines	Urine	All available
Barbiturates	Blood; urine	50 ml; all available
Heavy metals	Liver	500 grams
Arsenic	Hair	10 grams
Lead	Liver; urine	500 grams; all available
Mercury	Kidney	1 kidney
Inhaled poisons	Lung	1 lung
Volatile poisons	Brain	500 grams

A thumbnail rule as to quantity is "When in doubt, send more." A good practice for the physician performing the autopsy is to obtain as much as deemed feasible and immediately freeze these tissues. Then, upon further investigation, one can forward those specimens most likely to contain the suspected agent. Recently, 0.5 ml of serum was submitted with a request for tests as to barbiturates and narcotics. Obviously, the person submitting the request is unfamiliar with the type of analyses involved. From our viewpoint, we would prefer an excess of the sample and can always use a larger aliquot. Remember, we often are dealing with microgram quantities, and an inadequate specimen can result in failure to recover the substance. Although each laboratory may have slightly different requirements, exact information can be obtained from them directly.

Finally, how should these specimens be packaged? Place each organ in a separate, clean, glass vessel. Measure the amount submitted and note it carefully in the accompanying request. Seal each vessel. Whatever procedure is deemed most efficient should be used, remembering that some device should be employed to prevent tampering. A favorite method is the use of sealing wax marked with a distinctive seal.

Shipment in Medicolegal Cases

In order for the findings of the laboratory to be accepted as evidence, proof must exist that the specimens have been in proper custody.[5] This is commonly referred to as "chain of custody" or "chain of evidence." To meet these requirements, every person handling the specimens and packages must sign his name to this effect. The specimens cannot be mailed by regular or

ordinary mail. Registered mail, railway express, or air express are the only methods of shipment. If possible, a hand-carried specimen is most satisfactory. Remember, if there is any doubt as to the validity of the "chain of custody," the laboratory findings may be thrown out as evidence.

In an investigation of this type, the toxicologist generally is located at some distance from the originating agency. The specimens arrive with a request for certain determinations. Many times the request reads, "Toxicologic Examination." No other information is submitted to help. Where, then, does he start? An integral part of each case is a clinical history or autopsy protocol. Requests should be as specific as possible; the more specific the request, the more efficient the service.

DETERMINATIONS PERFORMED

Alkaloids

Urine appears to be the best specimen to work with. The alkaloids are determined by ultraviolet absorption spectra and paper chromatography. These compounds are tertiary amines and are basic in nature. Advantage is taken of their similarity for extracting them from urine. We have modified several procedures described in the literature.[6-8] Extractions are made from the urine at two different hydrogen ion concentrations (pH values). The extracts are then concentrated and chromatographed at four different pH values. After migration, the strips are air-dried and sprayed with an indicator reagent. Positive spots are shown as dark areas on an orange-pink background.

It has been shown that when a person takes codeine, some codeine is demethylated and excreted as morphine.[9] Figure 1 illustrates the recovery of both morphine and codeine from a patient who had taken only codeine. Further, one can distinguish between a person who has taken morphine and one who has taken codeine, as only morphine is excreted when morphine is taken. This was demonstrated by having a volunteer take 1/4 grain of morphine and collecting each urine specimen for the following 120 hours. Morphine was detected easily at 48 hours. Heroin *per se* is not recovered using the above procedure, but further work is being conducted along these lines.

A second procedure used for detection of alkaloids employs ultraviolet absorption spectra. In many cases, the absorption patterns of alkaloids are specific. The spectra are useful in making an initial screening of urine and blood specimens. The unknown is extracted with chloroform at acid, neutral, and basic pH values. The alkaloids are usually found in the basic fraction, whereas a substance such as salicylic acid is found in the acid fraction. The spectra obtained are compared with spectra of known

substances and a tentative identification made. This gives an indication of what must be done, *i. e.*, chromatography for alkaloids, or specific chemical determinations for other materials.

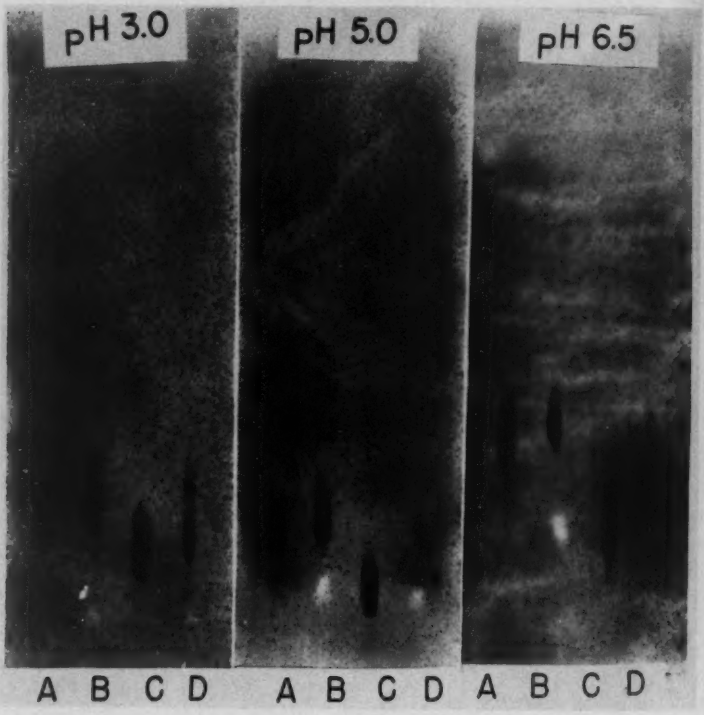

Figure 1. Results of chromatographic separation of urine extracts. At each pH, the codeine standard is shown as "A," the codeine extracted from suspected urine as "B," the morphine standard as "C," and the morphine extracted from suspected urine as "D." Note how the migration matches.

Ultraviolet spectrophotometry also is useful after chromatography. Positive stained areas are cut from the paper and eluted. The paper is treated with reagents to free the substance, which then is extracted and examined spectrophotometrically. The ultraviolet spectrum thus obtained is compared to spectra of known substances. The migration data from paper chromatrography in conjunction with an ultraviolet spectrum are sufficient to identify almost all of the basic substances of medicolegal interest. Figure 2 shows a comparison of standard strychnine with eluted strychnine. The similarity is excellent proof of identification.

With the use of increasing numbers of pharmacologic agents, the picture becomes more confusing. Antihistamines give similar

reactions. We have found that chromatography will easily separate them from the alkaloids, as the antihistamines migrate faster. With the advent of the tranquilizers, however, another problem arose. Several of these substances have properties similar to those of antihistamines and alkaloids, and stain with the indicator. We now are working on this class of agents. An example of the difficulties encountered is the inability to recover Sparine (brand of promazine hydrochloride) from a known urine sample, using the above technics. However, pure Sparine stains with the iodoplatinate indicator and migrates when chromatographed. The

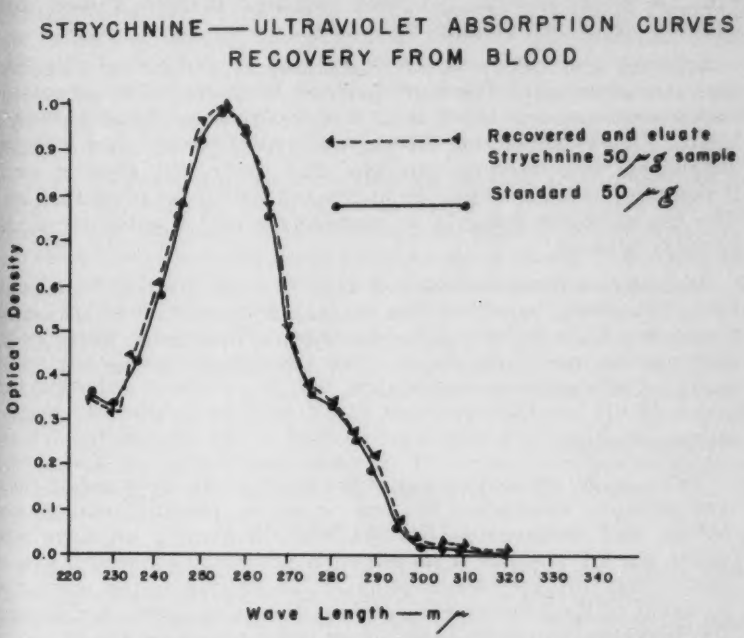

Figure 2. Comparative ultraviolet spectra obtained from a strychnine standard and strychnine recovered from blood. Note their similarity.

problem of the metabolism of these substances is an enigma, and just what the metabolic products will be and how they can be characterized and identified, remains for the future.

Barbiturates

The identification of barbiturates has been made simple by Goldbaum's excellent work.[10] Briefly, blood or urine is extracted at two different alkaline pH values and the ultraviolet spectra obtained. A ratio of optical densities at ten different wave lengths is made. These results quantitate the amount of barbiturate pres-

ent, and in several cases allow one to determine which class of barbiturate (*i. e.*, short acting or long acting) is present.

Heavy Metals[11,12]

This classification includes mercury, bismuth, antimony, arsenic, and lead. For the first four, a routine screening procedure, commonly referred to as Reinsch's test, is used. The specimen is hydrolyzed in HCl and a spiral of copper wire is placed in this mixture in an Erlenmeyer flask. This is boiled gently for one hour and the metal, if present, will be deposited on the copper wire. A silver coating indicates mercury, whereas a dark coat indicates antimony, arsenic, or bismuth.

Antimony and arsenic can be separated by performing Gutzeit's test. An organically digested specimen is treated with potassium iodide and stannous chloride in a specially constructed generator bottle. Zinc is added and the gas evolved is passed over a paper sensitized with mercuric bromide. The paper will show a stain if positive, and this stain can be treated further for identification. The use of known controls as standards gives an estimate of the quantity present.

Quantitative determinations of lead in urine are made routinely by a procedure based on the dithizone reaction.[13] Examination for other metals is by organic destruction with acid, followed by hydrogen sulfide precipitation. The precipitate is then analyzed by classical qualitative schemes.[14]

Volatile Poisons

This group includes many substances such as alcohol (ethyl and methyl), aldehydes, ketones, cyanide, phenols, carbon monoxide, and halogenated hydrocarbons. Recently, we have been using the Conway-cell microdiffusion procedure for initial screening.[15] This involves the placing of the sample in the outer compartment of the Conway cell, adding liberating agent, and trapping the liberated substance in the inner compartment by use of another reagent. The advantages are obvious: ease of sample preparation, use of small quantities, and rapidity of determination. Any positive reaction is investigated further by steam distillation and specific chemical tests of the distillate.

One exception to the above groups is carbon monoxide. If a determination of this substance is requested, it is quantitated by a procedure based on the difference of spectra of carboxyhemoglobin and reduced hemoglobin.[16]

Other Substances

A large number of other compounds, including amphetamine, bromides, organic phosphorous compounds, fluorides, and marihuana, have toxicologic significance. If a specific request is

made, an appropriate chemical procedure is employed in performing the test. We are, for example, able to screen amphetamine by its ultraviolet spectrum. This is then followed by a specific test for amphetamine.

REPORTS

The rapid reporting of results is of primary concern. This can be greatly expedited by making specific requests. The formal report rendered to the requesting physician gives the results of our findings in detail, but with no attempt at interpreting these results. It would be foolhardy if we were to attempt to determine the cause of death. The addict to arsenic, for example, would excrete huge amounts of this metal—amounts that would seem to us to be the cause of death. The requesting physician is in a better position to interpret our findings and there are available several texts in which toxicity of substances is reported.

Many substances never are identified because of improper specimens. They may be inadequate in amount, or obtained with too great a time lag (*e. g.*, those from narcotic users). Although several cases are on record with no specific cause of death, I am confident that if a foreign substance is present in adequate quantity, it will be detected. If there is an indication of substances other than those specifically requested, the toxicologist will pursue their identification. Several such cases are in our records. The toxicologist, however, is not an alchemist—there are no super-secret procedures for identifying toxic substances. He is a good analytical chemist and is just as concerned with solving the problem as is the person requesting it. The more help the requesting physician can render, the more accurate will be the results.

FUTURE PROSPECTS

Where will toxicology progress in the future? It is hoped that rapid, accurate screening procedures may become available. The advantage of such tests is self-explanatory. It also is hoped that these screening procedures can be followed by specific chemical tests which will effectively quantitate the compound. The more investigation done along the line of metabolism, excretion patterns, and identification, the sooner will be the solution of the many problems posed to the toxicologist. Forensic toxicology is no longer in the dark, but it still is standing in the shade.

SUMMARY

Proper submission of specimens cannot be overstressed, and they should be accompanied by a clinical history or autopsy protocol and a specific request. If there are medicolegal aspects to the case, a chain of custody must be maintained. The toxicologist can help solve many problems if care is taken to meet these requirements.

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HOW TO DRIVE TO THE AIRFIELD—SAFELY

"Most people are agreed that the average motorist has more dangers and decisions to face than the airline pilot (given relative competence in the respective fields). Pilots have told me that they are safer in their planes than when driving to the airfield. This is borne out by mortality statistics for motorcar travel and scheduled airline travel. Thus, the only sensible and practical rule for driving motorcars is, "No alcohol for twelve hours before driving," or at least to keep the blood alcohol below 0.03 per cent."

—HORACE E. CAMPBELL, M. D.
in *Rocky Mountain Medical Journal*
p. 59, Jan. 1958

SUBMARINE MEDICINE ON U. S. S. NAUTILUS AND U. S. S. SEAWOLF

JOHN H. EBERSOLE, *Lieutenant Commander, MC, USN*

IN THE past few years the highly specialized field of submarine medicine and submarine physiology has been deeply involved in the revolutionary changes brought about by the advent of the nuclear submarines, "Nautilus" and "Seawolf". Today there is more than promise that the problems of nuclear power will involve all fields of military medicine and this is not limited to military medicine alone, for the application of nuclear energy for civilian power, already in being in the United Kingdom, promises to bring these problems to civilian medical practitioners, particularly in the field of industrial medicine. While some of the problems met on "Nautilus" and "Seawolf" are limited to submarines because of their unique operational environment, many others apply equally to all reactor installations, either military or civilian, sea-going or shore-based. The experiences that submarine medicine has had in these initial years may, therefore, be justifiably utilized for a realization of the part that medicine will play in the nuclear age.

There are three important areas in which nuclear propulsion has strikingly added scope and depth to the field of submarine medicine. The first of these is a result of the new environmental situation created by reactor propulsion—an environment which bears little similarity to that of the conventional submarine. While understandable, it is erroneous to think of the medical problems of nuclear submarines as being a simple continuum of previous submarine problems to which has been added the factor of nuclear radiation. The environment of the true submersible, its effects and its control under prolonged submergence, represent a really new and unique entity, and radiation is but one of many factors.

The second significant change in submarine medical practice aboard a nuclear submarine lies in the necessity for strict supervision of radiation control measures during in-port periods. For the most part medical and toxicological problems of previous

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submarines have been minimal during in-port periods of maintenance. In contrast, in nuclear submarines, radiation control measures have actually greater significance during such periods than while at sea. It is during this time that reactor shield integrity may be broken in order to allow workmen access to the reactor system and to allow work on contaminated components in areas of radiation flux. Medical personnel must therefore be on the *qui vive* during any such period until the operation is completed in order to control exposure and to insure against spread of contamination. In quantitative terms, if alertness may be so quantitated, approximately four times more attention is required, based on relative exposure during maintenance as compared to that at sea.

The third, and perhaps most important, factor that has expanded the boundaries of submarine medicine is that on nuclear submarines a medical officer is directly assigned as a crew member, and is on board for all operations. Evaluation of the medical problems, therefore, no longer depends upon short term on-board observations in a guest capacity. The full impact of this intimacy is only beginning to be realized, but it can be assumed certainly that definition of the manifold problems cannot help but be improved. The rapid "break-through" in nuclear technology and the acceleration of new developments demand such intimacy for optimum results and maximum benefit to the submariner, whose health and efficiency are the prime interest of submarine medicine. This opportunity for daily, intimate, and long-term contact with the submarine and its problems may perhaps be ranked as the most important development in submarine medicine since its inception.

While this paper deals primarily with the radiation problem on nuclear submarines, it is necessary in introduction to reemphasize the poi nt that nuclear power represents more than just a radiation problem to submarine medicine. It is basically a study of the effect of a novel environment on the human organism.

THE SUBMARINE ENVIRONMENT

It has been stated previously that the nuclear submarine environment is unique; it is necessary, however, to reiterate this point, for it profoundly affects radiation control technique and, indeed, provides a leitmotiv in the formulation of the radiation hygiene programme.

The single most important factor in the environment with which we deal on nuclear submarines is the capability for long submergence independent of the Earth's atmosphere. All previous submarines have been dependent upon air, save for relatively short periods, rarely exceeding twelve hours, at which time

contact with the Earth's atmosphere was re-established. Once on the surface fresh air was circulated in the ship to dilute and displace toxic atmospheric elements accumulated in the ship during its submerged period.

Surfacing of the submarine at that time was required to run diesel engines, which, in turn, charged the electric storage batteries which propelled the ship when submerged. Operation of such diesel engines is an aerobic process—the combustion of oxygen and a fossil fuel.

The diesel snorkel has not significantly changed this situation for the snorkel tube, carrying air to the submerged submarine for her diesels, also carried fresh air to the ventilation system and to the crew as a secondary effect. Snorkelling must, therefore, be considered as a simple variant of full surface operations in which communication with the open atmosphere is maintained although the ship is submerged.

The impact of nuclear power lies in the fact that splitting or fission of the uranium atom to furnish heat for the production of steam is an anaerobic process—indeed, for technical reasons, oxygen must be excluded from the process. Given this as the basis for a propulsion system, rather than oxygen-dependent diesels, true submersible capability is achieved.

Visualize such a true submersible as a streamlined capsule operating beneath the ocean's surface. This microcosm, this sub-miniature world, must maintain an independent atmosphere and an ecology compatible not only with life, but with efficient combat life for the personnel contained within it. A most important limiting factor in this ecology is that such an atmospheric volume is contained and finite; therefore, little atmospheric dilution of any toxic air-borne substance can be expected. We will see later how this relates particularly to the control of air-borne radioactive contamination.

In such an environment three basic conditions must be met in order to support life:

(a) Continuous supply of oxygen to maintain normal atmospheric concentrations.

(b) Continuous removal of normal human metabolic products, i. e. carbon dioxide.

(c) Prevention of or provision for removal of any toxic substance released by ship's equipment.

As a corollary to these a vigorous and continuing study must be made of atmospheric conditions aboard to detect and quantitate new toxic elements. Experience has shown that many of the so-called "new" elements have existed previously in conventional submarines, but were either not recognized or were

quite properly disregarded, since significant concentration values were not obtained with the limited submergence times of the pre-nuclear period.

Many traps await the unwary in trying to forecast presence or degree of importance of a given toxic substance in such a finite environment. An example is that of carbon monoxide, the production of which was previously linked chiefly to diesel exhaust fumes. With the passing of diesel propulsion one might expect this problem to be minimized. On the contrary, tolerance concentrations (100 parts per million) have been reached within thirty hours submerged on nuclear submarines. The chief source now is tobacco smoke, a source not previously emphasized, yet of extreme importance with longer periods of submergence.

Another example of an apparently harmless product giving rise to trouble in this new environment is the evolution of radioactive radon gas originating from luminescent radium-painted markers. It has been standard practice for many years in our submarines to use radium-painted markers and dials for emergency illumination. Such radium, of course, will produce its radioactive daughter-gas, radon. Gaseous radon diffuses easily from apparently well-sealed components and enters the ship's atmosphere. Here it proceeds to decay into a long series of radioactive daughter elements which become associated with dust particles suspended in the air. They are then easily collected by the filtration devices which operate constantly to monitor the air for air-borne radioactivity. Figure 1 shows a rather dramatic increase in air-borne beta activity with time submerged as the result of only six small radium-painted switch markers being present on the submarine. Note the abrupt increase in air activity after submerging—a factor of more than ten in twenty-four hours. The curve shows the gradual levelling off as equilibrium is approached in about forty-eight hours. At equilibrium, levels are about thirty times higher than when surfaced. Apart from possible biological hazard this represents a serious nuisance because radiation monitoring equipment does not distinguish between such increases due to radon and that due to the much more serious condition of a reactor system leak. One would be justifiably quite concerned by such an increase if due to a reactor system leak. It is, therefore, necessary to initiate an immediate and complicated identification technique whenever such increases occur. The only solution is to remove all such radium sources from the ship, and, indeed, from the entire navy supply system to avoid their reappearance on board.

These problems, and others like them, have been solved for the most part by removal of the offending source, by insistence on more rigid leak tightness requirements in systems containing toxic materials or by substitution with less toxic materials,

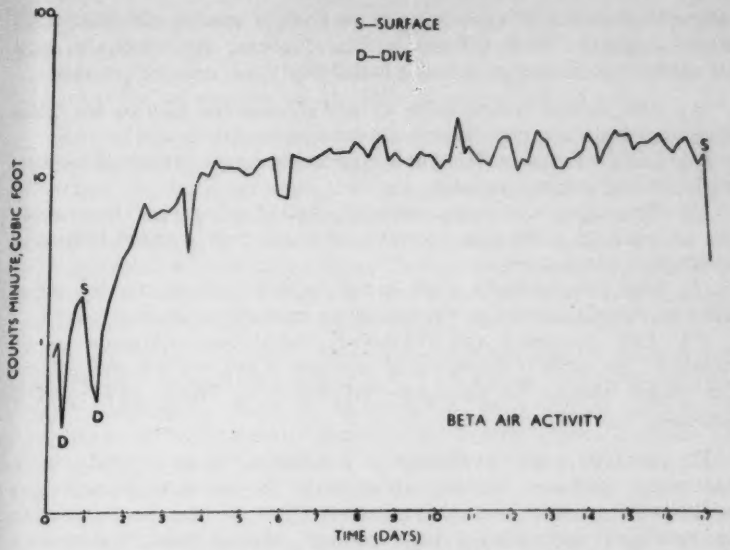

Figure 1. Radioactivity due to radium-painted markers.

and by development of removal systems such as the CO_2 scrubber. In the design of removal equipment medical personnel have a vital contribution to make. They must furnish the design engineer with the desired allowable concentration of the toxic substance. In the case of carbon dioxide, for example, it is not feasible to build equipment which will sustain zero concentrations; a compromise tolerance concentration must be used. Such tolerance concentrations, however, cannot be based on standard tolerances in the literature which apply usually to the eight-hour day, five days per week exposure time of industry. Aboard submerged submarines, where a 24 hours per day exposure is the case, lower tolerance limits must be applied. This principle equally is related to maximum permissible values for radiation levels as well as for toxic gases. It is, thus, one of the prime missions of submarine medicine to establish such limits by investigation and research and to communicate them to the design engineer.

The environmental factors at work here may equally apply to space medicine, and indeed, in many respects, one might simply substitute "space ship" for "submarine" in this discussion.

RADIATION IN THE SUBMARINE ENVIRONMENT

Radiation hygiene in a submarine, an environment radically different from that of land-based reactors, presents the necessity of adapting and modifying standard control techniques. In many

respects this novel environment is hostile toward efficient radiation hygiene. The following five factors, for example, will all operate to increase the shipboard radiation control problem:

(1) The closed atmosphere of a submersible allows for little dilution of air-borne radioactivity by dispersion in air.

(2) Lack of space for such requirements as decontamination stations and control areas.

(3) Proximity of living, eating, and food preparation areas to an operating reactor system with an ever-present potential contamination hazard.

(4) The submariner's work week, which is a seven-day week with no possible off-site recuperation from exposure.

(5) The constant and relatively rapid re-circulation of air through the ship's ventilation system when submerged allows for rapid spread of air-borne radioactivity from one spot to another.

If, however, one examines a submarine more closely there are many inherent factors, particularly in its architecture, that will tend to assist radiation control. First of all, the submarine is arranged horizontally like a long sealed tube. The reactor compartment section of the tube, the chief source of radiation, can affect personnel only within the compartment itself or immediately forward and aft of it. Shielding is thus simplified and the advantages of locating living areas with zero radiation levels either well forward or aft of the compartment, exploited. As far as the crew is concerned shielding in three planes only is vital, and full circumferential shielding of the system is not necessary.

An additional important factor is that our sealed tube is horizontally divided into a series of compartments by stout watertight bulkheads. This allows for rapid isolation of a given contaminated compartment simply by shutting a watertight door and securing ventilation to that area. In the case of the reactor compartment, ventilation supply and exhaust lines pass through the compartment without openings into it. Since this is the potential area of contamination, pick-up by the ventilation system can be avoided (fig. 2).

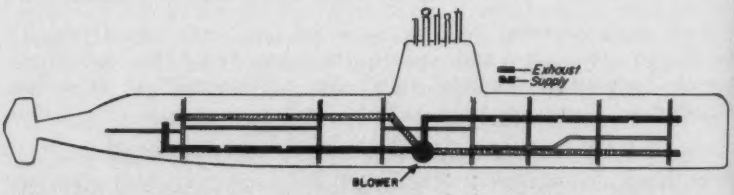

Figure 2. Submarine compartmentation and air recirculation.

Additional helpful factors are the small number of personnel in a submarine crew, which allows for ease of communication and control, and lack of multiple exits and entrances that must by guarded by monitoring stations in an industrial plant.

These advantages and disadvantages can be manipulated into an effective shipboard programme. For example, contamination control is built around the compartmentation system and its ease of isolation; occupancy of the reactor compartment is held to a minimum by placing master controls outside this area; contamination casualty regulations require rapid shutdown of the re-circulating ventilation cycle; protective clothing is dispersed fore and aft of the engineering spaces for accessibility.

Apart from control techniques themselves, considerable adaptation of radiation equipment is also necessary and laboratory techniques used on board must be modified to meet the peculiar environmental situation of a submarine. Radium calibration sources are prohibited due to the radon problem mentioned previously and cobalt 60 is substituted as a calibration source. Again, because of the explosion hazard and high oxygen consumption, open flames cannot be tolerated and evaporation of liquid samples must be done by infra-red lamps. Evaporation of large twenty-four-hour urine samples as a check on ingested activity is prohibited for aesthetic reasons in the confines of a submerged submarine, and must await an in-port period. At sea it would be done only on an emergency basis with an assured lowering of the popularity of medical department personnel among the crew. Volatile solvents in radio-chemical techniques must similarly be avoided. All radiation-measuring equipment must be rugged enough for use on board an operating combat ship, a requirement which, surprisingly, disqualifies many devices used in a shore-based installation.

One interesting technique modification is in the use of an end-window Geiger-Mueller tube for counting of liquid samples. In this a carefully measured 50 ml. aliquot of the liquid, usually reactor coolant water, is placed in a standard metal cup. The cup is positioned on a shelf beneath the Geiger tube. Accurate positioning of the cup in relation to the tube is important and is carefully checked with standard spacers and positioning pins. Under these fixed geometrical conditions the number of counts per minute obtained by counting the sample may simply be referred to a predetermined calibration curve of counts per minute versus microcuries per millilitre. If the calibration curve is based on an isotope whose energy approximates that of the sample very accurate results can be obtained to a level of 1×10^{-5} microcuries per millilitre. This is a simple, rapid technique and has the advantage of quickly being taught to untrained personnel. It was soon observed that in rough seas

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spillage from the cup would result from this procedure. Under such conditions the cup is covered with a thin film of Saran wrap, a cellophane-type material held firmly in place by a metal lip or rim which fits over the cup. Sensitivity loss when utilizing this is 10%, a reduction to 1×10^{-4} microcuries per millilitre as the lower limit of detection.

These are only a few of the necessary modifications to standard techniques, and, as in the case of radiation control procedures, the submarine milieu is all-important in determining the degree and type of modification necessary.

THE REACTOR

Before discussing the personnel exposure problem aboard nuclear submarines it is necessary to describe the reactor system.

A water-cooled reactor may be considered simply as a collection of uranium atoms. Bombarded by neutrons, the uranium atoms fission, or split, and release a tremendous amount of radiation and kinetic energy as heat, which can be removed by water flowing through the reactor lattice. The two atomic fragments remaining after the parent uranium atom is split are the fission daughters, and are intensely radioactive, emitting both gamma and beta radiation. These fission daughters cause *residual reactor radiation* long after the reactor is shut down. The reactor, then, is responsible both for prompt fission radiation (gamma and neutron) and residual radiation (gamma and beta). These are not the only sources of radiation for the reactor as it operates produces high levels of neutron radiation in its vicinity. These reactor neutrons will activate stable non-radioactive atoms present in the coolant water flowing through the reactor lattice.

As water flows through the reactor the temperature of the water is raised by the fission process and this heat, in turn, is transferred to a steam generation system through a heat exchanger or boiler. The reactor coolant water leaving the heat exchanger is then propelled back through the reactor by a pump. This closed cycle operation of coolant water is illustrated in figure 3. There are two important points to note about this system—first, the piping carrying this coolant water is leakproof; secondly, the steam generated in the heat exchanger is not radioactive. Note that the radioactive coolant water "sees" the steam only through the walls of the heat exchanger; there is no direct contact between radioactive water and the steam. This steam can thus be easily transferred from the reactor area without shielding and can be used to turn a conventional steam turbine.

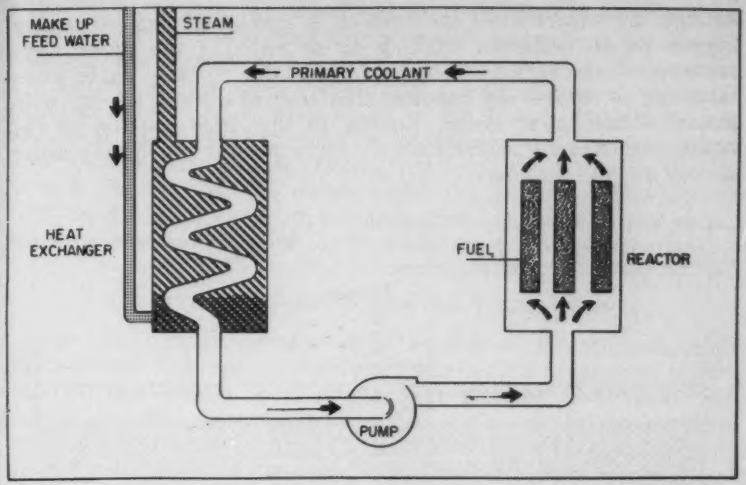

Figure 3. Basic reactor system and coolant cycle.

Circulating in the coolant water are the neutron-activated radioactive atoms we have mentioned previously. The metallic radioactive atoms will tend to stick on the inner surface of the piping, an important phenomenon, having an effect both in raising radiation levels in the area, and in necessitating precautionary measures for contamination control whenever the system piping is opened. These radioactive atoms in the system piping continue to radiate after the reactor is shut down, and they are chiefly responsible for the gamma radiation levels in the compartment at that time. The residual fission radiation from the fission daughters in the reactor itself, being well shielded, makes little contribution. In the case of the longer-lived radioactive atoms in the coolant water, there will tend to be increasing build-up with time so that static conditions will not be met in regard to radiation dose in this area, but will tend to increase.

The compartment containing the reactor system is a section of the submarine termed the reactor compartment. This compartment, essentially a right cylinder, is divided horizontally by a deck forming an upper and lower reactor compartment. The deck is actually a thick shield, below which is placed the reactor and all the coolant system (fig. 4).

Note from figure 4 that the upper reactor compartment sees no contaminated coolant water, only non-radioactive steam. Some gamma and neutron radiation will enter the upper level

through the shield when the reactor is operating, but not in any degree which prohibits working in or manning the upper compartment. The highest level of radiation in the upper compartment is above the reactor area and sharply falls off with distance from that point. Levels in the after section of the upper compartment at full power, for example, are of the order of only 5 mrem per hour.

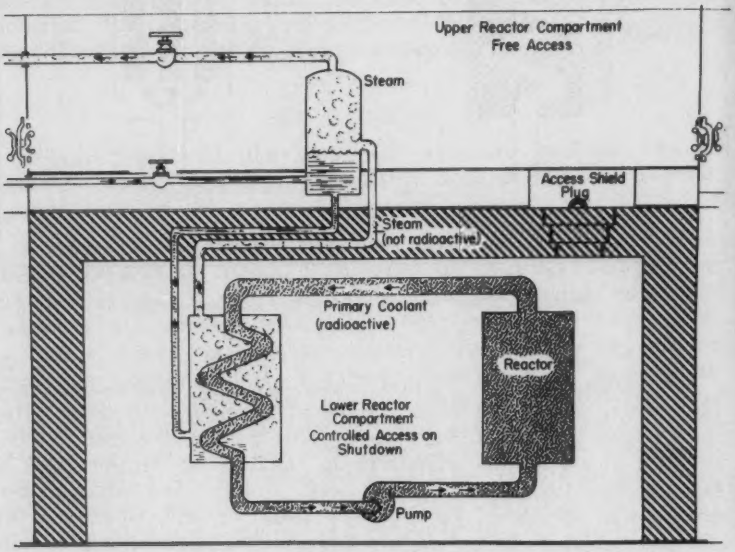

Figure 4. Reactor and its shielding.

It must be emphasized that the reactor compartment is the only area on the ship where a radiation flux exists. All other compartments are similar to those on conventional submarines. Outside of the reactor compartment, crewmen, when submerged, receive less radiation than when ashore, due to the shielding effect of the water on cosmic radiation. This effect is noted on background radiation which decreases to a third of surface values with increases in depth of the submarine.

To return to the lower reactor compartment—the majority of the radioactivity in the coolant water has a short half life, and, because of its rapid decay, the lower area can be entered after reactor shut-down. While some reactor residual radiation remains, the chief source of radiation is gamma from the "plate-out" activated atoms inside the piping. Normally, there will be no exterior contamination present unless the system has been opened previously and contaminated coolant water spilled.

Prior to entry into the lower reactor compartment after reactor shutdown, ship's personnel are preceded by medical department members who survey and monitor the area, checking for surface contamination, air-borne radioactivity, and degree of potential exposure. Permissible stay times in the lower compartment are determined and requirements for protective clothing formulated from this information. Monitoring stations are also established at exit points from the compartment and personnel leaving the area carefully checked for contamination. The monitoring points are also used as change areas if protective clothing is required.

RADIATION EXPOSURE LIMITS—THEIR MEANING

One of the often misunderstood aspects of radiation exposure is a faulty concept of maximum permissible exposure levels, particularly in relation to presence or absence of clinical findings. In dealing with any potentially toxic material industrially, be it lead, organic solvents, or radiation, it is necessary for operational purposes to compromise between zero exposure and the levels known to cause detectable biological effects. This compromise value, often called tolerance, is usually placed well below the threshold of minimum clinical change by a large factor—providing a threshold clinical response is typical of the toxic element in question.

In arriving at such a maximum permissible value, one uses historical observations, human clinical data, animal experimentation and laboratory data. For continuous industrial application the permissible exposure arrived at must be well below the threshold known to produce detectable change even if the exposure should last over the entire work life of the individual. This is usually accepted as being thirty years in duration.

Since for many clinical effects the rate of exposure is equally as important as the total integrated amount received over a given period, permissible levels may be expressed in terms of a rate. In the case of radiation the rate of total body exposure rather than the total dose is the more important, except for genetic, and possibly longevity effects. For example, 40 roentgen of total body gamma radiation received over a period of eight years will produce no effect on haematology of the individual, yet the same dose, if delivered in minutes, will produce demonstrable findings. In this latter case the time-dose relationship is such that the rate of tissue regeneration is exceeded by the rate of tissue damage.

The permissible exposure basically used in shipboard shielding design is 300 mrem per week measured in air. Note that this is not a wartime, or single emergency, or casualty exposure, but an industrial type application for continuous operation over a work lifetime. If 25 to 40 rem total body radiation is required

as the threshold dose to initiate leukopenia—one of the most sensitive of biological indicators—it is obvious that one cannot depend upon clinical laboratory procedures to control radiation exposure at or below the 300 mrem/week tolerance level. In the haematological example the threshold of a sensitive biological indicator is 150 times greater than the maximum allowable weekly exposure of 300 mrem, far too high to be of any value.

The important and often misunderstood point is that *personnel exposure control and exposure measurement at or below tolerance levels is entirely dependent upon instrumentation. Clinical laboratory procedures are of no value in this regard.* This point is emphasized because of the repeated questions, not limited to laymen, concerning clinical findings in our personnel, particularly in relation to haematology. The lack of reality in these questions is obvious when the exposure pattern on "Nautilus" and "Seawolf" is analysed. This point is emphasized because of the potential danger inherent in the false idea that routine blood counts constitute a radiation hygiene programme. If such a programme were mistakenly used as a control measure, gross over-exposure by present tolerance standards would result.

A second point that requires emphasis is that, since permissible levels are well below the biological threshold, cumulative effects by definition cannot occur, since rate of tissue and cellular repair will always exceed rate of damage. Note this holds true only for effects that show a threshold, and does not apply to such non-threshold phenomena as genetic change where cumulative effects can occur independent of rate.

THE EXPOSURE RECORD—"NAUTILUS" AND "SEAWOLF"

The preceding statements become more emphatic when the personnel exposure data of "Nautilus" and "Seawolf" are analysed. At the presently accepted permissible exposure of 300 mrem per week, during the fifty-week period of one year a man may receive 15,000 mrem (or 15 rem). Recent recommendations from the National Committee on Radiation Protection may, in effect, officially reduce the weekly permissible exposure to 100 mrem per week. On a yearly basis this would be 5,000 mrem (or 5 rem) per man per year. Bearing the figures of 15,000 and 5,000 mrem per year in mind, note the following average exposures:

(1) "Nautilus" in 1955 -- 173 *mrem per man per year*
(2) "Nautilus" in 1956 -- 210 *mrem per man per year*
(3) "Seawolf" in 1957 -- 204 *mrem per man per year*

"Seawolf" exposure data is extrapolated from data obtained during the first six months of her first fully operational year.

These figures of average yearly individual exposure at their maximum represent 1.4% of the official permissible exposure and less than 5% of the proposed new permissible exposure level.

If, rather than the average exposure, the maximum individual yearly exposure is used a wide differential still exists between the actual level and the maximum permissible level. The following represent the highest individual yearly exposures recorded:

(1) "Nautilus" in 1955 - -	1,438 *mrem per year*
(2) "Nautilus" in 1956 - -	2,100 *mrem per year*
(3) "Seawolf" in 1957 (extrapolated)	1,126 *mrem per year*

Taking the highest figure, these maximum exposures represent values of either 14% or 44% of the maximum permissible exposure per year.

Figure 5 illustrates an important pattern of this exposure in depicting the distribution of yearly dose among the ship's population. It should be noted here that almost 50% of the crew receive no measurable exposure. The remainder of the crew spend varying periods of time in the reactor compartment and, therefore, receive some exposure. This is the only section of the ship where exposure can be received due to the conservative shielding practice described previously. The data shown in figure 5 is from the 1955 data of U. S. S. Nautilus but has held true since that period for both ships.

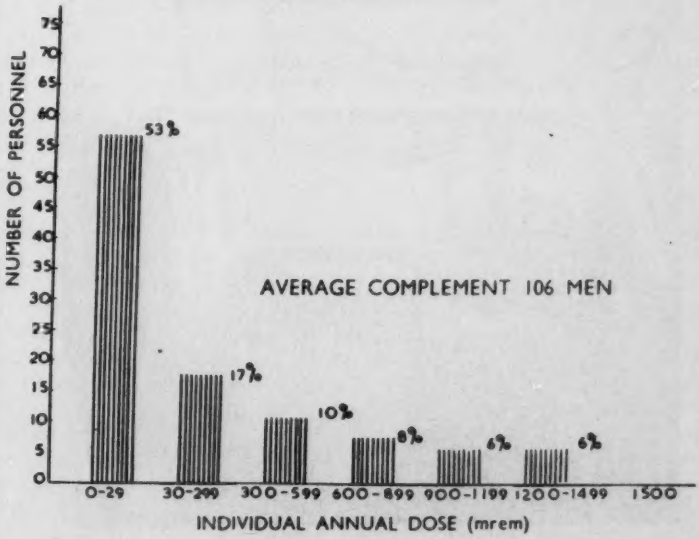

Figure 5. Distribution of individual exposure during 1955.

This exposure record serves to emphasize the fact that all of our experience to date is well below both the level of clinical effect and of maximum permissible exposure values.

INSTRUMENTATION

In the absence of any dependable clinical effect to quantitate human exposure our dependence upon instrumentation is great. The data given above, for example, were obtained from personnel film badges worn by all hands on board. Such personnel exposure is measured both by the film badge and pocket dosimeter. The ship maintains its own photodosimetry programme, including capability for full processing of the film badges. Radiation monitoring equipment, counter-scalers for sample counting, radiochemical equipment, radiation sources, film processing tanks, and other equipment are located in a small, compact laboratory under medical department cognizance duplicated in both ships. Figures 6 and 7 show views of the laboratory. In addition to the concentration of analytical equipment in the laboratory, protective clothing, including filter masks and emergency radiation measuring devices are dispersed throughout the ship.

Figure 6. Radiation laboratory.

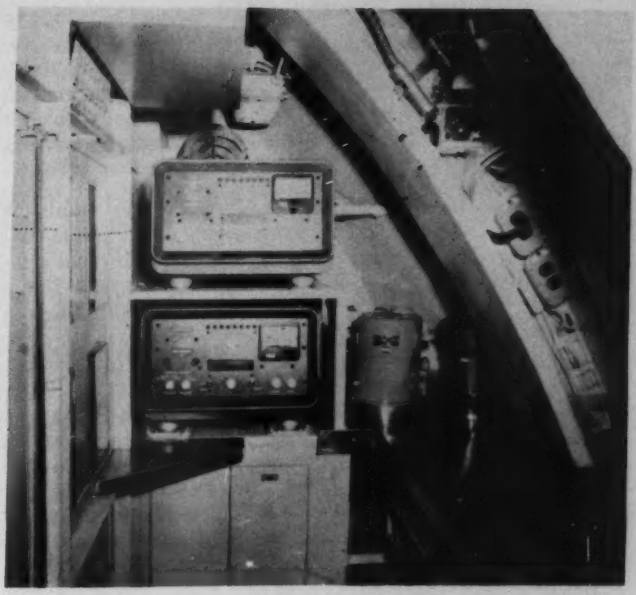

Figure 7. Radiation laboratory; another view.

It has been emphasized that these instruments, rather than any known biological changes, are required to quantitate personnel radiation exposure at the sub-threshold levels encountered in nuclear submarines. Such equipment may appear deceptively simple in operation but requires a thorough knowledge of its limitations, capabilities, and eccentricities for maximum usefulness.

Let us analyse some of the general problems associated with personnel dosimetry in order to point out the pitfalls in using instrumentation. Consider, for example, the film badge and pocket dosimeter. These devices are worn by all the ship's personnel when aboard and form the basis for personnel exposure records. The film badge is a metal holder, divided into a shielded portion and an open window portion. This division of the badge into two sections allows the film contained in the badge to differentiate between beta and gamma radiation by the response of the portion of the film below the shield compared to that below the open window. This also allows for some differentiation of thermal and fast neutrons if the shield is cadmium or some other element which captures thermal neutrons. In the case of beta-gamma radiation the film, after developing, presents a density proportionate to the amount of radiation seen. The

degree of density of the emulsion is determined by a densitometer, and the density obtained referred to a density-dose calibration curve. The calibration curve itself is based upon exposure of several films to a known standard radiation source, determination of the density for each known dose, and plotting the results as a curve. Such a curve must be made on each batch of film used.

The pencil-like pocket dosimeter is a device much like a simple gold leaf electroscope. When held up to light a fibre is visible in the eye-piece against a small scale reading 0 to 200 milliroentgen. Ionizing radiation passing through the dosimeter removes an electric charge on the fibre causing it to move across the scale in the manner of the gold leaf in a discharging electroscope. The fibre can be reset to zero by re-charging the dosimeter after any desired time or dose interval. Removal of the charge, and hence a positive reading, can occur due to insulation leakage known as "drift". Usually this is at a very low rate, but must be determined on each dosimeter. Calibration against a standard radiation source is also necessary as with film. A characteristic of dosimeters is sensitivity to mechanical trauma—an important negative characteristic aboard a ship where rough treatment may be expected.

Many variables affect results and influence interpretation in both instruments. In the case of film, storage at recommended low temperatures is important. Film storage must also provide for zero radiation exposure which must be checked by processing control film. Calibration conditions for both devices must be carefully considered, including freedom from backscatter. Both film and dosimeters are energy-dependent, and for this reason the calibration source must emit energies approximating those to be met in the field, a difficult achievement. In the case of dosimeters, the drift rate must be repeatedly checked as insulation properties may change with time and environmental conditions.

If it is assumed that all of these factors have been adequately controlled, many important variables remain to be considered. First of all, both these devices will usually be worn clipped to the shirt front. In this position they do not measure a pure air dose as required by definition of the roentgen, but a complex dose disturbed by body backscatter. While one may minimize this factor by calibrating with a phantom, the angle of incident radiation in the field may differ significantly from that of the calibration situation; this is not a predictable variable within accuracy limits in the shipboard situation, but varies from position to position and with the attitude of the wearer.

If these factors are accepted, one faces an important problem in interpretation of the depth dose. The film badge is worn on the body surface and, as such, measures a surface dose which will be significantly modified by several centimetres of tissue before reaching a depth such as the median sagittal plane. The relationship between surface and depth dose can be computed, but the relationship will vary markedly with the energy of the radiation, with variation in tissue density due to presence of bone or air, and with angle of incidence of the radiation among other factors. A specific instance of large error, for these reasons, exists in those cases where the primary radiation enters posteriorly and the devices are worn anteriorly, a practical situation in lower reactor compartment work. An additional factor lies in the fact that, while total body exposure is the entity of interest, only a few square inches of body surface is covered by the film badge and dosimeter. A narrow beam may, therefore, be missed entirely, or, if detected, will be overemphasized in relation to total body exposure.

If all of these possible variables and conditions are accepted, one is still faced with even further variables in the technique of film processing itself. These include control of purity of water used in mixing processing solutions, adequacy of darkroom conditions, and control of solution temperature during processing. Temperature control alone is a formidable problem and must be maintained rigidly throughout the processing solution with avoidance of any layering effect because temperature changes during processing will affect the emulsion as well as radiation.

Considering all of these many variables inherent in only two of the instruments used, it is not surprising that there is a search for some concrete biological change as a means of quantitating exposure to ionizing radiation. Interpretation of data obtained from such equipment requires a broad knowledge of both physical and biological factors. This is probably the strongest argument for the utilization of a medical officer in this field. Radiation is not an entity whose hazard can be simply evaluated by a glance at a meter or recording of a number, but requires careful consideration of many physical and biological factors. This is particularly important as a result of recent trends toward lower permissible exposure values, as instrument accuracy becomes more strained at the lower limits of sensitivity.

MEDICAL DEPARTMENT DUTIES

The medical departments of both ships consist of a submarine medical officer and two hospital corpsmen, although more corpsmen may be assigned from time to time for training purposes.

The medical officer, besides his regular submarine medicine training, will have received at least an academic year of training in nuclear medicine, and will usually have had several months' experience at an operating land-based reactor prototype. The corpsmen have received at least nine months of training in radiation hygiene techniques, and also participitate in the course in nuclear engineering given to all engineering ratings.

While at sea one of the three members is on watch in the laboratory at all times. During his watch he is responsible for following a schedule of various radiation checks. For example, every four hours portable air samples are taken in the engine room and reactor compartment and processed in the laboratory, several check points in the reactor compartment are spot-monitored for gamma and neutron radiation levels as a check on shield integrity, constant monitoring equipment through the ship is checked, read, and recorded every watch, liquid samples from various portions of the engineering plant are processed and counted on a watch basis in order to maintain a constant record of radioactivity present. All radiation measuring devices must be checked daily for accuracy with standard radiation sources. Weekly, all compartments are wipe-sampled as a check on surface contamination. Every two weeks personnel film badges are collected, processed, and results recorded. When submerged, in addition to the radiation measurements, determinations of oxygen, carbon dioxide, carbon monoxide, and other gases are made every two hours.

During in-port periods if work is scheduled in the lower reactor compartment, particularly if disassembly of the system is involved, the workload increases markedly. For, in such a period, the control of contamination in the confined space of a submarine represents a great challenge. In such a period monitoring points must be manned, work times determined in radioactive areas, protective clothing requirements decided upon, and transport of contaminated material supervised. Decontamination facilities may have to be established. The situation is never static. Each task requires its own analysis and solution.

THE FUTURE

The problems of the future with the expansion of the nuclear navy are:

(1) Need for extensive training of personnel and development of shore-based facilities for handling repair and maintenance of nuclear ships, especially in processing of contaminated equipment on the ship and on the base; establishment of dosimetry and monitoring facilities for contaminated laundry; use of material decontamination techniques.

(2) Development of more accurate instruments for relating radiation measurements to true biological dose, particularly in the field of neutron flux measurement.

(3) Development of long-term training programmes for both officer and enlisted medical personnel in the field of radiation hygiene.

(4) Continuing research on the effects of prolonged submergence, particularly in the identification and quantitation of all atmospheric elements built up under such circumstances.

But these are problems limited to the navy where nuclear power is in being rather than in potentiality—what of the significance to the civilian medical profession as a whole? A recent article in *Nucleonics* magazine, demonstrates the dramatic increase in the number of operating civilian reactors by 1960. With such acceleration medical problems are bound to appear in this area, and can potentially involve all of us, if in nothing more than in allaying the chronic semi-hysterical outlook of the public in any matter concerning nuclear radiations.

Nuclear power is the most promising development to meet the challenge of diminishing fossil fuel supplies. The events in the Middle East stress the World's dependence upon fossil fuels and the consequences of any diminished supply of them. Yet, diminish they must, and at a rapid rate by the early twenty-first century, with consequent lowering of industrial potential and standards of living if substitutes are not available. Great Britain has already launched a large-scale civilian nuclear power programme.

Specifically, the physician interested in industrial medicine will be deeply involved in evaluating and establishing future radiation control programmes, the traumatic surgeon may find wound contamination a new factor, the ophthalmologist will be used in physical screening of personnel for posterior subcapsular opacities, the internist will be involved in diagnostic problems, not the least of which may be emotional in origin in relation to radiation; haematologists will also play a part.

We must not, then, consider this a limited field, confined to a handful of military specialists; but a field of potential future significance to us all. Apart from the specialized problems mentioned, the profession should be cognizant of this technology and its effects simply to answer the questions from a public beleaguered with conflicting statements related to weapons and weapon effects, so often confused with reactor radiation problems.

It would seem prudent to incorporate such subject matter into medical school curricula as soon as possible, and perhaps into present industrial medicine courses, perhaps as part of radiology,

by any method which will assure our capability of dealing with the problem.

DISCUSSION

In reply to a large number of questions by Squadron Leader T. C. D. Whiteside, Air Commodore D. A. Wilson, Dr. B. W. Soole, Rear-Admiral G. A. M. Wilson, Dr. D. W. H. Barnes, Mr. D. E. Barnes, Professor G. P. Crowden, Surgeon Captain C. B. Nicholson and others, Lieutenant-Commander Ebersole said that body odours were overcome largely by the use of the filtration units already installed for removing CO_2 and CO from the atmosphere and by the submarine's ventilation system. The crew also became immune to the residual submarine odour during a long cruise, although others became aware of it when they went ashore. Dispensing with diesel propulsion had not changed this characteristic submarine smell which permeated clothing and was probably contributed to by a number of chemical factors which had not as yet been identified.

He was convinced of the need for the Naval Medical Department to be given full responsibility for the control of the environmental factors, including the radiation hazard, which were encountered during prolonged submergence in nuclear-powered submarines especially during the developmental period. This allocation of responsibility might not hold, however, for nuclear-propelled surface ships. The engineers had their hands full with their own technical problems in submergence and it would be unfair to expect them to give the necessary weight to the human factors which these obviously merited; and they might at times "rush in where angels fear to tread!" The commanding officer needed the authoritative advice of a medical officer who was technically familiar with the many complex problems involved, particularly as the total situation had not yet been evaluated.

In the United States Navy submarine medical officers and hospital corpsmen were trained in submarine physiology and plant construction as part of their initial course of instruction before they volunteered for nuclear-powered submarines and underwent further training. They had to know the component parts of the engineering plant and even to take part in routine watchkeeping duties. This additional training had paid off time and again during the development stage and early operations of U. S. Submarines Nautilus and Seawolf.

In reply to Dr. Soole Lieutenant Commander Ebersole said that saturated caustic soda was used for fission product analysis in place of ammonia hydroxide—a nasty substance to handle in a rolling submarine. Mineral acids were substituted for volatile

organic acids such as glacial acetic acid. Pulse height analysis was not used for identifying specific isotopes. There were at present difficulties in the use of scintillators which might be overcome.

The neutron problem was first tackled by the contractor who was required to shield the reactor to ensure that not more than 10% of the radiation dosage was due to neutrons. The B.F.3 tube instruments for thermal neutron estimation and Radioactive Products Incorporated Model E.1 fast neutron dose rate meter were used as routine monitoring instruments. Neutron film badges (Eastman Kodak N. T. A. emulsion of 40 micron thickness) were always worn but they were only developed if the gamma dose exceeded 200 mr in a two-week period.

Neutron film development was more complex than estimating gamma dosage, as it involved the use of a microscope and oil immersion techniques.

In reply to Dr. Barnes he showed a picture of the ship's sick bay which was kept quite separate from the radiation laboratory. There was, however, very little sickness in submarines apart from the customary respiratory epidemics at the beginning of a cruise before the crew became immune to each others' strains. The number of injuries sustained on the bridge on the surface in conventional submarines was greatly reduced in nuclear-powered submarines which spent very much longer periods submerged.

In reply to Mr. Barnes he pointed out that radiation dosage was not a function of the shield entirely, as the greater exposure occurred during maintenance periods when men were beneath the shield. Little was to be gained by shaving a small amount of lead off the shield under existing circumstances, especially as at a later date the submarine might well be required to carry a large amount of lead ballast when it went to sea, a fraction of which could have been incorporated in the shield. There would be a gain from reducing the size of the reactor compartment but this would also reduce the accessibility of the component parts within it.

EPIDEMIOLOGIC STUDY OF TUBERCULOSIS IN THE U. S. NAVY AND MARINE CORPS

II. Service Characteristics and Adequacy of Case-Finding Methods*

PHILIP R. BECKJORD, *Colonel, MC, USA*
PHILIP E. SARTWELL, *M. D.*

STATUS by service in Regular or Reserve category was studied because reserve personnel, having the possibility of one or more tours of active duty interrupted by long periods of civilian life, might be more heavily exposed while not in uniform. However, reserve personnel constituted only 8 per cent of the total and were represented about equally in the study and control groups. The percentages of reservists shown in the control group for Navy and Marine Corps agree closely with actual average percentages of these components shown in official Navy personnel reports.[15]

Service interrupted by periods of more than one month was found to have occurred rarely in the control group but was more frequent in the study group; thus, among enlisted men, tuberculin-negative at entry, interrupted service was encountered in 2.2 per cent of the study group and 0.3 per cent of the comparable controls, a statistically significant difference. The difference becomes unimportant, however, if those whose tuberculin status on entry was positive or unknown are included. The limitation of the time period of service considered evidently minimized the number of personnel included who had interrupted service, and the importance of this factor remains in doubt.

CORPS OR BRANCH OF SERVICE, SERVICE OCCUPATION, SHIP DUTY, AND GRADE

In 1953, official reports show that the enlisted male medical and dental personnel of the entire Navy constituted 4.2 per cent of the average male enlisted strength of the service during the

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From Office of The Surgeon General, Department of the Army, Washington, D. C., and School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Md.

This study was supported by a contract with the Research and Development Division, Office of The Surgeon General, Department of the Army.

year, all periods of service considered.[4] Among the control group of this study, this occupational category comprised 5.5 per cent; thus, in respect to furnishing the proper proportion of medical and dental enlisted personnel, the representativeness of the control group again appears satisfactory.

Table 17 shows that 5.1 per cent of the study group were medical and dental enlisted personnel, a figure slightly though not significantly smaller than the controls. Even if we substitute the figure of 6.6 per cent so as to include all those cases whose records were not received, the excess of this occupation in the study group is still small in comparison with the control group. Britten[7] noted a higher tuberculosis attack rate in medical personnel of the Navy in 1949, but the present findings are not in agreement with his finding; they are, of course, limited to men with less than six years of service. Calculation of true attack rates was not possible in the present study because denominators were not available.

TABLE 17. *Corps or branch of service of male enlisted personnel*

Corps or branch of service		Study group		Control group	
		Number	Per cent	Number	Per cent
Navy					
Recruit	A	5	1.6	8	2.2
	B	2	1.1	4	1.6
Medical and dental	A	16	5.1	20	5.5
	B	12	6.5	16	6.3
Aviation	A	39	12.4	75	20.5
	B	21	11.4*	52	20.6*
General service	A	252	80.5	261	71.3
(360)	B	149	80.5*	180	71.1*
Others	A	1	0.3	2	0.5
	B	1	0.5	1	0.4
Subtotal	A	313	100.0	366	100.0
	B	185	100.0	253	100.0
Unknown	A	1		0	
	B	0		0	
Total	A	314		366	
	B	185		253	

"A" refers to the group, regardless of tuberculin sensitivity.
"B" refers to tuberculin-negative individuals.
*$P < 0.05$

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Aviation Group

The aviation group constituted 19.1 per cent of all Navy enlisted males of all periods of service in 1953, and in table 17 it is seen that the control group representation is 20.5 per cent, a close approximation. In the study group and basic study group the proportion is significantly lower, suggesting that men serving in this occupation are at lower risk of contracting tuberculosis. An explanation for this is not readily apparent; possibly aviation personnel, as a total group, are not in as close physical contact with their fellows as are ship personnel. Physical standards for the enlisted aviation group are the same as for the Navy enlisted personnel, except for a small number (less than 10 per cent) who are directly engaged in flying activities.

The General Service Group

In 1953, this group comprised 74.7 per cent of all Navy enlisted males of all periods of service,[4] while 71.3 per cent of the controls were classified as general service. The proportion in the basic study group is 80.5 per cent, significantly higher than the comparable controls.

The general service group, as a whole, largely serves on ships, with only about 20 per cent not having ship service (table 18). On the other hand, it is seen that in the basic study group the proportion having no ship duty is significantly lower, in fact, 8.8 per cent. Thus, it appears that general service personnel with ship duty seem to be especially at risk of tuberculosis.

In seeking an explanation for the apparently higher risk shown for men having ship duty versus those with none, table 19 was prepared to compare length of service prior to suspect diagnosis. There is little difference, the medians for the two categories in the basic study group, general service Navy, being 2.5 and 2.4 years, respectively. Difference in length of service exposure, then, cannot account for the disparity; ship service in itself may, therefore, be a decisive factor.

An examination of the type of ship served (table 20), reveals that the largest differences occur in the aircraft carrier group, possibly indicating a greater risk of tuberculosis for men on these vessels, and in amphibious vessels, which seemingly afford less. These figures, while not statistically significant, are in agreement with impressions voiced by several senior medical officers of the Navy. Such factors as crowding, occupation while on ship duty, number of men per vessel, and length of time at sea may warrant further investigation.

A more detailed analysis of the general service group, divided into its component occupational specialties, is shown in table 21. The risk of tuberculosis appears less for the engineering

TABLE 18. *Ship duty in service prior to suspect diagnosis, male Navy general service (360) enlisted basic study group*

Category	Cases		Controls	
	Number	Per cent	Number	Per cent
A. Ship duty				
Yes	134	91.2	142	79.8
None	13	8.8*	36	20.2*
Subtotal	147	100.0	178	100.0
Unknown	2		2	
Total	149		180	
B. Amount of ship duty				
Less than 50 per cent	30	22.6	34	24.5
50 per cent or more	103	77.4	105	75.5
Subtotal	133	100.0	139	100.0
Unknown	1		3	
Total	134		142	
Median percentage	73		71	

*P <0.05

TABLE 19. *Length of service of male enlisted general service basic study group according to experience with ship duty*

Length of total service	Cases				Controls			
	Ship duty		No ship duty		Ship duty		No ship duty	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Less than 1 year	3	2.3	1	7.7	9	6.5	12	33.3
1-2 years	33	24.8	2	15.4	36	25.9	11	30.6
2-3 years	61	45.9	8	61.5	57	41.0	9	25.0
3-4 years	30	22.6	2	15.4	37	26.6	3	8.3
4 years or more	6	4.5	0	0.0	0	0.0	1	2.8
Subtotal	133	100.0	13	100.0	139	100.0	36	100.0
Unknown	1		0		3		0	
Total	134		13		142		36	
Median in years	2.5		2.4		2.4		1.5	

TABLE 20. *Type of ship service, male Navy general service enlisted basic study group*

Type of ship	Cases		Controls	
	Number	Per cent	Number	Per cent
Aircraft carrier	31	23.1	18	12.7
Cruiser	13	9.7	12	8.4
Destroyer	30	22.4	27	19.0
Amphibious	15	11.2	31	21.8
Auxiliaries	35	26.1	39	27.5
All others*	10	7.4	15	10.5
Total	134	100.0	142	100.0

*Battleship, submarine, command, service, mine, and patrol.
Differences in these subcategories are not significant.

TABLE 21. *Service occupation, male Navy general service enlisted basic study group*

Service occupation	Cases		Controls	
	Number	Per cent	Number	Per cent
Deck and ordnance	28	18.9	22	15.5
Engineering and hull	27	18.2	47	33.1
Administrative and clerical	34	23.0	37	26.0
Potential strikers	52	35.1*	19	13.4*
All others**	7	4.8	17	11.9
Subtotal	148	100.0	142	100.0
Unknown	1		38	
Total	149		180	

*$P < 0.001$
**Construction, precision equipment, steward, electronics, miscellaneous.
Differences in these subcategories are not significant.
$n = 4; \times 2 = 25.75$

and hull servicemen, again for reasons presently unknown. Although the risk among potential strikers appears highly significant, there is some doubt as to the accuracy of occupational classification in this study. As is seen by the relatively large number of unknowns in table 21, information about service occupation was frequently unavailable for the control group and the available data, particularly on the strikers, were less precise in comparison with the study group. Potential strikers are usually

young enlisted men, not long out of "boot camp" who are understudying for rated occupational positions or are acting as general-duty hands. Their occupational duties are of many varieties and include those of many of the other job categories listed in the table.

Analysis of service occupation and ship duty for the Marines was not rewarding. Almost all (98.3 per cent) men in the Marine Corps were in the so-called "460 Group" which is, broadly speaking, general service. The Marine Corps is primarily a fighting force whose logistical support is largely performed by the Navy; occupational specialities in the force are relatively few. With minor exceptions, Marines are shore based and the question of Marine Corps ship service is not believed pertinent to the analysis.

The distribution of enlisted grades in the service showed no remarkable difference between the study and control groups.

Basic Training Camp

The "boot camp" or basic training center is the place where the Navy or Marine Corps recruit first comes into close contact with thousands of other young men from many parts of the country. This period of training lasts two or three months or longer and presents a favorable opportunity for the spread of upper respiratory disease. While the preinduction medical screening procedures should have all but eliminated the possibility of a recruit with tuberculosis infecting others at camp, there could conceivably be cases among the training cadre which could infect the recruits. To see if this might be the case, table 22 was prepared. The results are negative. The various training camps furnished cases of tuberculosis in about the same proportion as they trained recruits, year by year.

Marital Status and Mode of Living

These factors were considered in an effort to estimate the time servicemen spent away from the milieu of service life. All men, of course, have off-duty periods but married men, particularly in the higher grades, often live with their wives and children and not in barracks. The question has, therefore, certain constant aspects. Despite the fact that records containing positive information showed that about 22 per cent of the men in both groups were married, less than 6 per cent lived with or visited their families or relatives.

As expected, almost all (well over 90 per cent) of both groups lived in barracks or ship. That a slightly but significantly higher proportion in the basic study group lived with their families is not due to better history taking by interns; this information was based on personnel records equally appraisable in both groups.

Although this finding might lead one to suspect that familial contact with tuberculosis might explain the difference, it was found that only one of the 13 initially tuberculin-negative tuberculous men who frequently visited their families had a history of contact with a known tuberculous family member while in service.

TABLE 22. *Year of induction and place of basic training of male enlisted basic study group, by service*

Training center		1948	1949	1950	1951	1952	1953	1954	Total	Per cent
Navy										
Great Lakes	S	3	5	17	26	11	0	1	63	34.2
	C	0	2	16	53	14	4	0	89	35.2
San Diego	S	1	4	20	29	25	4	1	84	45.6
	C	1	2	30	34	30	6	1	104	41.1
Bainbridge	S	0	0	0	8	16	0	0	24	13.0
	C	0	0	1	12	23	6	3	45	17.8
Other	S	0	0	11	2	0	0	0	13	7.1
	C	0	0	4	10	1	0	0	15	5.9
Subtotal	S	4	9	48	65	52	4	2	184	100.0
	C	1	4	51	109	68	16	4	253	100.0
Unknown	S	0	0	1	0	0	0	0	1	
	C	0	0	0	0	0	0	0	0	
Total	S	4	9	49	65	52	4	2	185	
	C	1	4	51	109	68	16	4	253	
Marines										
San Diego	S	1	0	3	3	10	4	0	21	45.6
	C	0	1	4	0	15	10	2	32	41.0
Parris Island	S	0	0	3	7	9	5	1	25	54.4
	C	0	2	8	16	12	6	1	45	57.7
Other	S	0	0	0	0	0	0	0	0	0.0
	C	0	0	0	0	1	0	0	1	1.3
Subtotal	S	1	0	6	10	19	9	1	46	100.0
	C	0	3	12	16	28	16	3	78	100.0
Total	S	1	0	6	10	19	9	1	46	
	C	0	3	12	16	28	16	3	78	
Grand total	S	5	9	55	75	71	13	3	231	
	C	1	7	63	125	96	32	7	331	
Per cent by year	S	2.2	3.9	23.8	32.5	30.7	5.6	1.3	100.0	
	C	0.3	2.1	19.0	37.8	29.0	9.7	2.1	100.0	

S = Basic study group.
C = Comparable control group.

Foreign Service

During the years covered by this study, most service personnel on foreign duty were either in the southeast Asia area or in the Atlantic, Caribbean, and Mediterranean areas. The data were examined to see if foreign duty, which presumably in some areas involved contact with people in whom the incidence of tuberculosis was higher than in the United States, exerted an effect. Tables 23 to 27 present the findings in this respect. As was the case in considering ship duty, it is the general service group of Navy enlisted man, and also Marines, who are of chief interest here.

TABLE 23. *Foreign service experience of male enlisted basic study group*

Category	Cases		Controls	
	Number	Per cent	Number	Per cent
Foreign service	171	81.8	170	62.7
No foreign service	38	18.2*	101	37.3*
Subtotal	209	100.0	271	100.0
Unknown	22		60	
Total	231		331	

*P <0.001

Table 24 shows the distribution of the cases and controls according to the total number of years of service and whether or not the men had had foreign service. For both groups, the percentage with a record of foreign service increases with length of service. Except in the case of men with less than one year of service, where the numbers are quite small, a larger percentage of the study group than of the controls had had foreign service. In order to remove the effect of service, the percentages of men who have had foreign service were adjusted to a standard population, the combined number of study and control men with each specified period of total service. Adjusted percentages are 77.6 and 65.1 for the study and control groups, respectively. It therefore appears that foreign service had an influence on the development of tuberculosis in men who were uninfected upon entry into the service, although the number of controls for whom this item was unknown is disturbingly large.

The time from last satisfactory x-ray examination to suspect diagnosis was examined and found to differ but little between

men who had had and those who had not had foreign service, the medians being 15.0 and 13.6 months, respectively. Navy and Marine personnel had generally similar distributions.

Navy case-finding activities for men serving overseas seem to compare reasonably well with programs for men serving only in the continental United States. This is further substantiated by the fact that the extent and activity of tuberculosis was about the same in the two groups at the time of diagnosis.

TABLE 24. *Foreign service experience according to length of total active service prior to suspect diagnosis, for male enlisted personnel of the basic study group*

Length of service (months)	Cases			Controls		
	Total Number	With foreign service		Total Number	With foreign service	
		Number	Per cent		Number	Per cent
0-12	13	1	7.7	43	6	14.0
12-24	58	45	77.6	73	44	60.3
24-36	90	79	87.8	93	68	73.1
36-48	38	37	97.4	57	48	84.2
48 and over	10	9	90.0	5	4	80.0
Total	209	171	81.8	271	170	62.7
Adjusted* per cent with foreign service			77.6			65.1
Difference between adjusted percentages				12.5		
Standard error of difference				3.4		
Probability of a difference as great as, or greater than, this arising by chance				.001		

*Adjusted to number of men in study and control groups combined in each length-of-service class.

Whether foreign service was mainly aboard ship or on a shore base seems to have no influence in respect to disease among enlisted Navy men, although one might suppose that shore-based sailors would have more contact with civilians.

The areas of foreign service were studied in some detail. There was difficulty in deriving exact places from the records, and frequently notations of multiple areas of foreign service were troublesome in compilations. Because of the small numbers involved it was found impractical to be very specific in analyzing geographic areas. Consequently, the data were consolidated in table 25. These data indicate that the risk of infection is significantly higher in the Japan-Korea and Mediterranean areas for Navy personnel. Inasmuch as essentially all Marines with foreign service were assigned to the Pacific, and most of these to Korea, no statement can be made regarding their relative risks.

TABLE 25. *Area of longest continuous foreign service for male enlisted basic study group, by service*

Area*	Navy				Marine Corps			
	Cases		Controls		Cases		Controls	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Pacific	83	61.0	79	62.2	33	94.3	40	93.0
(Japan, Korea or both)	(62)	(45.6)**	(32)	(25.2)**	(30)	(85.7)	(33)	(76.7)
Atlantic	7	5.1	11	8.7	1	2.9	0	0.0
Caribbean	9	6.6	18	14.2	1	2.9	3	7.0
Mediterranean	23	16.9	9	7.1	0	0.0	0	0.0
Others and combinations of above	14	10.3	10	7.9	0	0.0	0	0.0
Subtotal	136	100.0	127	100.0	35	100.0	43	100.0
No foreign service	27		69		11		32	
Unknown	22		57		0		3	
Total	185		253		46		78	

*Broadly defined as including land areas touching on these waters.
**$P<0.001$; $\chi^2 = 29.99$; $n = 5$.

The difference between foreign areas did not seem to be due to differences in total length of service or length of time spent outside the United States.

In the basic study group the time from the start of the longest period of foreign service to the date of suspect diagnosis was determined as well as the duration of the longest period of foreign service (table 26). The medians of these two variables for the Navy enlisted basic study group are 19 and 15 months, respectively, and for Marines they were 14 and 13 months, respectively. The median duration of longest foreign service for the service categories of the comparable controls (tuberculin negative) was 16 months for the Navy and 12 months for the Marine Corps; thus, in this regard, there was no appreciable difference in length of foreign service between the basic study group and its comparable controls.

The finding in the basic study group that Marine Corps cases were brought to suspect diagnosis faster (by 5 months) than Navy men, after beginning foreign service, warranted investigation. It appeared possible that the Marines may have had a more severe infection and were more frequently discovered because of symptoms. While this seems to be the case, at least in relation to symptoms (table 27), nevertheless, again, the numbers are too small for adequate analysis.

Marines spent less time overseas than Navy men, and although it might be suspected that they had the benefit of earlier x-ray screening on return to the United States, it has already been

TABLE 26. *Duration of longest continuous period of foreign service for male enlisted basic study group, by service*

Months	Navy				Marine Corps			
	Cases		Controls		Cases		Controls	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Less than 6	12	17.6	4	7.3	4	12.9	9	29.0
6-12	16	23.6	15	27.3	8	25.8	7	22.6
12-18	13	19.2	12	21.8	19	61.3	13	41.9
18-24	14	20.6	12	21.8	0	0.0	2	6.4
24-36	11	16.2	10	18.2	0	0.0	0	0.0
36 and over	2	2.8	2	3.6	0	0.0	0	0.0
Subtotal	68	100.0	55	100.0	31	100.0	31	100.0
No foreign service	27		69		11		32	
Unknown*	90		129		4		15	
Total	185		253		46		78	
Median in months	15		16		13		12	

*Includes those with unknown foreign service and those with foreign service whose length of foreign service was not determined.

noted that the overseas annual chest x-ray program compared well with that in the continental United States. Further, as shown in table 27, only 29 per cent of the Marines with foreign service were brought to diagnosis by routine annual x-ray.

Further analysis of reasons leading to a suspicion of tuberculosis and of the stage of the disease at diagnosis, for larger groups in this study, is presented in a later section.

Combat

During the period 1950-1953, many Marines were engaged in ground combat in Korea. The question as to whether the privations of combat affected the incidence of tuberculosis in this group was of interest. Definite information as to participation in combat was elusive in the medical records. Among those for whom it was known there was no significant difference between the study and control groups.

Only one or two of the Marines in the study were noted to have been wounded in action.

Prisoners of War

Throughout the literature on tuberculosis in the military, frequent mention is made of its high incidence among prisoners of war.[16] Of the approximately 800 Navy and Marine Corps men missing in action in the Korean War, only 184 (157 Marines, 27 Navy)

TABLE 27. *Analysis of possible factors influencing diagnosis of tuberculosis following foreign service for male enlisted basic study group, by service**

Cause of suspect diagnosis	Classification of disease at final diagnosis									
	Pulmonary tuberculosis active						Other tuberculosis		Total	
	Minimal		Moderately advanced		Far advanced					
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Navy										
Physical symptoms and signs	0	0.0	11	37.9	9	31.0	9	31.0	29	42.0
Routine annual x-ray	9	30.0	15	50.0	4	13.3	2	6.7	30	43.5
All other	3	33.3	6	66.6	0	0.0	0	0.0	9	14.5
Total	12	17.6	32	47.1	13	19.1	11	16.2	68	100.0
Marine Corps										
Physical symptoms and signs	0	0.0	6	33.3	6	33.3	6	33.3	18	58.1
Routine annual x-ray	5	55.5	3	33.3	1	11.1	0	0.0	9	29.0
All other	1	25.0	2	50.0	0	0.0	1	25.0	4	13.0
Total	6	19.4	11	35.5	7	22.6	7	22.6	31	100.0

*For those whose duration of foreign service was known (see table 26).

were repatriated in the large prisoner exchange of August-September, 1953. Only one of this number, a Marine Corps private, was found to have incurred tuberculosis while in captivity, based on findings of the physical examinations of U. S. prisoners performed immediately after repatriation. No other former POW's were noted, in this study, as having developed the disease in service up to 31 December 1954, the terminal date for the study. It is not known, of course, how many men developed tuberculosis and died while in the hands of the enemy or how many developed the disease after leaving the service following repatriation; the latter figure would require a search of Veterans Administration files and was not attempted in connection with this study.

OTHER CHARACTERISTICS OF THE STUDY GROUP

Time from Suspect Diagnosis to Final Diagnosis

The remainder of this report is devoted to a further consideration of the tuberculosis case series selected for study, with a view to learning their clinical character and evaluating as far as possible the adequacy of case-finding methods employed.

The time elapsing from suspect diagnosis to final diagnosis was studied in terms of the median number of months required

by the Navy Medical Department to study male enlisted cases of tuberculosis and make the final diagnosis. This might be important in relation to changes in extent of disease occurring during clinical study. The median for the male enlisted study group falls under one month; 81.5 per cent of the cases were given a final diagnosis by the end of the third month. It is therefore considered that the classification of the disease at final diagnosis may be used as essentially synonymous with stage at discovery.

In seven cases, 12 or more months elapsed between suspect and final diagnosis. These were mostly men who had a suspicious routine film recorded while at sea or on the move, and through administrative delays were not admitted to a hospital until much later.

Reasons for Suspecting Tuberculosis and Classification of Disease at Final Diagnosis

The event bringing the tuberculous individual to medical attention is important in tuberculosis control. The study results confirm the value of routine annual chest x-ray programs in the Navy and Marine Corps.

The routine annual chest x-ray was responsible for the discovery of 35.6 per cent of the entire enlisted study group (table 28). It is disappointing, however, that an even larger number (46.0 per cent) were discovered as a result of symptoms or signs of the disease. The finding that only 9 per cent were picked up on discharge examination is remarkable; if there had been no annual chest x-ray program, the figure would undoubtedly be much higher.

Minimal tuberculosis was largely discovered by routine x-ray (60.8 per cent) and far-advanced disease by symptoms or signs (73.9 per cent). Moderately advanced disease was detected about equally through x-ray (41.7 per cent) and by symptoms (36.4 per cent). Notable, also, was that "all other" tuberculosis was mainly disclosed following symptoms (82.3 per cent); about 50 per cent of this category is made up of tuberculous pleurisy (BDN 0041, 0042[17]). The 220 cases of moderately and far-advanced active pulmonary tuberculosis together here represent 55.5 per cent of all tuberculosis, and the 79 cases of minimally active disease 19.9 per cent. Tuberculous pleurisy accounts for about 9 per cent of the total.

There was no distinct difference in the stage of disease at final diagnosis depending on whether the individual was tuberculin positive or negative at entry (table 29), and it does not appear that those who reacted strongly developed relatively more severe forms of the disease than did those with weaker reactions. However, "all other" types (chiefly pleurisy with effusion) were

relatively more frequent among those who were tuberculin negative or, at least, doubtful reactors. This is consistent with the view that tuberculous pleurisy as the first manifestation of the disease generally occurs soon after infection.

TABLE 28. *Classification of disease at final diagnosis in relation to causes of discovery for all enlisted personnel*

Cause of discovery	Pulmonary tuberculosis, active								Other forms*		Total	
	Minimal		Moderately advanced		Far advanced		Arrested					
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Physical symptoms or signs	11	13.9	55	36.4	51	73.9	0	0.0	65	82.3	182	46.0
Routine annual chest x-ray	48	60.8	63	41.7	14	20.3	11	61.0	5	6.3	141	35.6
Discharge examination	13	16.4	14	9.3	1	1.4	3	16.6	4	5.0	35	8.8
Unrelated illness	2	2.5	11	7.3	1	1.4	1	5.6	3	3.8	18	4.5
Special hazard examination	3	3.8	4	2.6	1	1.4	1	5.6	0	0.0	9	2.3
Re-enlistment examination	2	2.5	2	1.3	1	1.4	1	5.6	1	1.3	7	1.8
Other	0	0.0	2	1.3	0	0.0	1	5.6	1	1.3	4	1.0
Total	79	100.0	151	100.0	69	100.0	18	100.0	79	100.0	396	100.0

*Includes BDN 0041 (Pleurisy, tuberculous, with effusion).

Demonstration of the Organism and Tuberculin Sensitivity at Final Diagnosis

Tuberculin sensitivity on entry into service apparently was not a significant factor in demonstration of the organism at diagnosis (table 1).

Only about 81 per cent of all cases in the study group, tested with PPD (first strength) and read, reacted positively at final diagnosis (table 30). However, at least 54 (83 per cent) of the nonreactors to this dose were positive when injected with PPD (second strength). Seven (2.5 per cent) of 267 enlisted males from whom *Mycobacterium tuberculosis* was recovered did not react to either strength PPD. The total sensitivity, both strengths considered, was in the order of 97 per cent for the entire group, and this was true of the organism-positive cases considered separately.

Sensitivity to Coccidioidin and Histoplasmin at Final Diagnosis

For some years the Medical Department of the Navy has routinely used, in major hospitals, the coccidioidin and histoplasmin tests in examining all patients suspected of having tuberculosis. Recently, in several of the Navy training centers these tests also have been given to recruits, and reactions entered on the individual's immunization register.

The status of sensitivity to these tests in the study group is shown in table 31. Contrary to expectation, there was less sensi-

TABLE 29. *Classification of tuberculosis at final diagnosis by tuberculin reaction on first entry into service, for all personnel in study group*

Classification	Negative		1 plus or doubtful		2 plus		3 or 4 plus		Total positive or doubtful		Unknown		Total	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Active pulmonary														
Minimal	46	19.5	7	18.9	6	22.2	8	26.7	21	22.3	17	22.7	84	20.8
Moderately advanced	89	37.7	16	43.2	10	37.0	13	43.3	39	41.5	24	32.0	152	37.5
Far advanced	42	17.8	7	18.9	5	18.5	3	10.0	15	15.9	12	16.0	69	17.0
Inactive pulmonary	8	3.4	0	-	1	3.7	3	10.0	4	4.3	6	8.0	18	4.4
All other	51	21.6	7	18.9	5	18.5	3	10.0	15	16.0	16	21.3	82	20.3
Total	236	100.0	37	100.0	27	100.0	30	100.0	94	100.0	75	100.0	405	100.0

TABLE 30. *Tuberculin sensitivity at final diagnosis—male enlisted study group*

Sensitivity	*Myco. tuberculosis* found		*Myco. tuberculosis* not found		Total	
	Number	Per cent	Number	Per cent	Number	Per cent
PPD, first strength (0.00002 mg)						
Positive	226	84.6	74	72.5	300	81.3
Doubtful	4	1.5	0	0.0	4	1.1
Negative	37	13.8**	28	27.5**	65	17.6
Total tested and read	267	100.0	102	100.0	369	100.0
PPD, second strength (0.005 mg)*						
Positive or doubtful	30	81.1	24	85.7	54	83.1
Negative	7	18.9	4	14.3	11	16.9
Total tested and read	37	100.0	28	100.0	65	100.0
Total positive or doubtful to PPD, first or second strength	260	97.4	98	96.1	358	97.0

*In nonreactors to PPD, first strength.
**$p < 0.01$

TABLE 31. *Status of sensitivity to coccidioidin and histoplasmin at final diagnosis in relation to demonstration of* Myco. tuberculosis, *enlisted study group*

Sensitivity to fungi	*Myco. tuberculosis* found		*Myco. tuberculosis* not found		Status unknown		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Coccidioidin								
Positive	35	13.6	13	15.7	0	0.0	48	13.8
Doubtful	1	0.4	0	0.0	0	0.0	1	0.3
Negative	222	86.0	70	84.3	7	100.0	299	85.9
Subtotal	258	100.0	83	100.0	7	100.0	348	100.0
Unknown	31		16		1		48	
Total	289		99		8		396	
Histoplasmin								
Positive	64	24.7	15	18.1	2	28.6	81	23.2
Negative	195	75.3	68	81.9	5	71.4	268	76.8
Subtotal	259	100.0	83	100.0	7	100.0	349	100.0
Unknown	30		16		1		47	
Total	289		99		8		396	

tivity to histoplasmin in the organism-negative group than among those from whom *Myco. tuberculosis* was recovered. The difference is not statistically significant, but at least suggests that histoplasmosis was not erroneously diagnosed as tuberculosis with any appreciable frequency.

DISCUSSION

Several of the positive findings of this study are confirmatory of the work of others. Palmer, Jablon, and Edwards[11] have demonstrated the difference in relative incidence of tuberculous disease in previously infected and uninfected men. The question of whether reactors or nonreactors are at greater risk of tuberculous disease has long been discussed. Studies of nursing students, as summarized by Daniels,[18] generally have indicated that nonreactors were more vulnerable; this also has been true among inmates of institutions where the infection risk is high. In other groups where the risk is not so high, the nonreactors have fared better, as in this study. One explanation for this apparent paradox, as suggested by Zacks and Sartwell,[19] is that in the community the reactor frequently is a person with heavier risks of re-exposure to *Myco. tuberculosis* in past and current environment than are found in the environment of the nonreactor; also there is the opportunity for endogenous development of disease in the reactor. The nonreactor, placed in a situation where risk of infection is high, on the other hand, has to endure the extra hazard of disease which accompanies the first few months after infection, and which the reactor has already passed.

Inasmuch as the environment of reactors and nonreactors in military service is similar, we may conclude that it is the endogenous spread of *Myco. tuberculosis* from their inapparent foci that is responsible for this greater incidence of tuberculosis in reactors. While the risk of reactors in this situation is greater than that of nonreactors, it must not be forgotten that the actual number of cases among the initial nonreactors in this study constituted over 70 per cent of the total, in consequence of the high proportion of men who were uninfected at entry (over 90 per cent).

The findings with respect to the constitutional factors of height and weight are confirmatory for at least three earlier studies, as previously mentioned. The influence of foreign service, ship duty, and naval occupation has not, it is believed, been previously demonstrated.

The study suggests that the methods employed by the Medical Department of the Navy to control tuberculosis are useful and reasonably efficiently performed. It is believed that the use of the annual chest x-ray on all personnel has brought about the early discovery of a large number of cases of tuberculosis that otherwise would only have been picked up at re-enlistment or discharge. This is shown by the fact that 35.6 per cent of all cases in the study group were revealed by the routine annual chest x-ray and only 10.6 per cent through re-enlistment and discharge examinations.

SUMMARY AND CONCLUSIONS

A study has been made of cases of tuberculosis diagnosed in a two-year period (1953-1954) in the U. S. Navy and Marine Corps among personnel with less than six years of military service. The primary purpose of this study was to determine epidemiologic factors of importance in the occurrence of tuberculosis in a military service. A secondary purpose was to evaluate the tuberculosis control measures that were employed. As controls for this study, a sample of all cases of acute appendicitis, occurring in these services during the same time period and matched with the study cases of tuberculosis for length of service, was utilized. The most striking differences between the tuberculosis cases and the controls were as follows:

1. A much higher proportion of the tuberculosis cases than of the controls were tuberculin positive on first entry into service. The incidence of tuberculosis is estimated to have been 3.6 times greater in reactors to tuberculin than nonreactors. The frequency of nondisqualifying pulmonary lesions identified on routine roentgenogram at entry was higher among tuberculin positives of the study group of tuberculosis cases than among the nonreactors.

2. The proportion of nonwhite persons was higher in the study group of tuberculosis cases.

3. Comparison of the height and weight distribution revealed an excess of tall men and of underweight men in the tuberculosis group.

4. Occupational analysis revealed an excess of tuberculosis in the general service group of the Navy, particularly in the category known as "potential strikers" and, also within this group, in men who had ship duty.

5. There was a marked excess of Navy personnel having had foreign service, particularly in the Japan-Korea and Mediterranean areas, in the tuberculosis group.

6. Analysis of data relevant to effectiveness of Navy case-finding procedures, such as the interval from last negative film to development of tuberculosis, the stage of the disease, and symptomatic status, indicates that procedures for early diagnosis are reasonably satisfactory.

7. This study has again demonstrated the importance of constitutional factors, of factors related to prior infection with *Mycobacterium tuberculosis,* and of factors concerned with the military environment in the epidemiology of tuberculosis in the Armed Forces.

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IS DIPHTHERIA CONTROL IN DANGER?

"It is distinctly possible that our excellent record of diphtheria control is in jeopardy, because in many communities the proportion of immune individuals has fallen far below 70 per cent. We face the interesting paradox of having produced a predominantly susceptible population as a result of immunization programs. When diphtheria was rampant, as high a proportion of the adult population as 90 per cent had acquired a natural immunity. The natural booster effect of a large reservoir of infection maintained this level of immunity. Today a great many children are immunized in infancy. This immunity often is not maintained either through booster injections or through natural exposure; five years after primary immunization, one-third of the persons, not having received booster injections, again are susceptible to diphtheria as indicated by the Schick test. Persons who never have been artificially immunized are frequently susceptible throughout their adult life because of the decreased opportunity to acquire natural immunity. . . .The consequence of this might be predicted: 'Although adult cases have dropped fourfold from the previous decades to the past decade, deaths have decreased but slightly, and an ominous rise in adult fatality is noted. . . .For higher age groups case fatalities began to decrease, but have taken a sharp rise in the last decade. Late years have shown a conspicuous number of diphtheria cases in old people.' "

—C. ARDEN MILLER, M. D.
in *Postgraduate Medicine*
p. 447-448, Nov. 1957

Clinicopathologic Conference

U. S. Air Force Hospital, Maxwell Air Force Base, Ala.*

VAGINAL BLEEDING AND RENAL FAILURE

Summary of Clinical History. A 16-year-old housewife initially was admitted to a civilian hospital in November 1952. Her complaints at that time were nausea, vomiting, edema, and vaginal bleeding of about one month's duration.

She had had the usual childhood diseases without sequelae. There was no history of scarlet fever, nephritis, rheumatic fever, or serious illness other than the present one. She did not use alcohol, tobacco, or drugs.

History was obtained from the patient's mother and from old clinical records, as the patient was comatose on admission and could not give any information. The patient's mother stated that the patient was well until late October 1952, when she began having nausea, vomiting, and generalized edema. She had been married approximately 2½ months at that time and had not menstruated since marriage, but she had always been irregular since menarche at age 14. In early November the patient began to have vaginal bleeding, and a private physician who was taking care of her thought that she might have had a miscarriage but he was not sure. He also told the patient's mother that the patient had leukemia. The bleeding was severe enough to require approximately one blood transfusion per day for 15 days. Later in November, she had a more severe hemorrhage which necessitated uterine packing. There was no further vaginal bleeding as far as is known.

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From December 1952 until 22 March 1953, the patient was hospitalized continuously in a civilian hospital. No records are available from that hospitalization, but apparently the patient had a refractory anemia which required repeated blood transfusions.

On 27 March 1953, the patient was transferred to the U. S. Naval Hospital, Memphis, Tenn., and while there continued progressively downhill with frequent nausea and vomiting. The blood urea nitrogen rose from 56.4 mg per 100 ml on admission to 109 mg per 100 ml on 21 April. Chlorides varied between 125 and 150 mEq per liter. The patient received daily infusions of 10 per cent dextrose in water and numerous blood transfusions. No sodium chloride was given. She was digitalized shortly after admission, but this was discontinued after several days. Phenobarbital was given to control restlessness and convulsions. Blood pressure was recorded at 160/115 mm Hg on occasions. The patient was reported to have had episodes of pulmonary edema and hypertensive crises with convulsions. She was transferred to the Walter Reed Army Hospital on 3 May 1953. For several days prior to her transfer, she had frequent epistaxes and regurgitation of blood from the stomach.

Physical Examination. Admission examination revealed a well-developed, edematous, semicomatose white woman who responded only to painful stimuli by crying. Her blood pressure was 120/60 mm Hg; pulse, 68 per minute; temperature, 97°F. Head and neck: There was no nuchal rigidity; the thyroid was not enlarged and there was no venous distention in the neck. The pupils were dilated and reacted sluggishly to light. Funduscopic examination was negative. There was crusted blood in both nares. Chest examination was negative. The heart showed minimal cardiomegaly, and a grade II rough precordial systolic murmur with a questionable rub over the base of the heart was heard. Two fingersbreadth hepatomegaly was noted. The spleen was not palpable and there were no abnormal abdominal findings. Pelvic examination was within normal limits. There was sacral edema and 3 plus pitting edema of the feet, ankles, and pretibial areas. Reflexes were slightly hyperactive bilaterally. The patient responded only to painful stimuli. The plantar response was normal. There was no significant lymphadenopathy.

Laboratory Studies. Hematocrit was 42 per cent, hemoglobin was 13 grams per 100 ml, and the red blood cell count was 4,350,000 per μl. The white blood cell count was 8,000 per μl, with 88 per cent neutrophils, 11 per cent lymphocytes, and 1 per cent basophils. The sedimentation rate was 42 mm per hr. Urinary specific gravity was 1.010 with 4 plus albumin, no reducing substance, and numerous red and white blood cells on microscopic examination. Blood urea nitrogen was 114, rising to 150 mg per 100 ml. Serum sodium was 107, rising to

125 mEq per liter; serum potassium varied between 3.6 and 5.4 mEq per liter; chlorides rose from 52 to 76 mEq per liter; CO_2 stayed between 17.3 and 18.5 mEq per liter; calcium varied between 2.9 and 3.6 mEq per liter. Urinary output was noted to be between 425 and 525 ml per 24 hours. During electrolyte replacement, the patient gained at least 1 3/4 pounds. The electrocardiogram was interpreted as "compatible with severe electrolyte disturbances."

Course in Hospital. The patient remained comatose or semicomatose until her death. She was given 300 ml of 5 per cent saline solution intravenously on admission, but without clinical change. Penicillin and streptomycin were started. Another 300 ml of 5 per cent saline solution to which was added calcium gluconate was given on the second day, again without improvement. On 5 May 1953, the morning of her death (3rd hospital day), the patient had a short episode of tonic and clonic movements of her extremities. Her blood pressure was stable at levels about 165/45 mm Hg with rare transient falls to values as low as 120 systolic. In the afternoon, she again began to have convulsions, and 150 mg of Amytal Sodium (brand of amobarbital) was given by slow intravenous injection; however, the convulsion continued, and after 7 to 8 minutes, the patient died.

DISCUSSION

Doctor Hoefle:* The illness of this 16-year-old white female dependent dates back to October 1952. Our records are not clear regarding that illness and up to the time of her admission in March 1953, but we know that she had nausea, vomiting, and generalized edema. She had an episode of vaginal bleeding in November 1952 and, apparently, a refractory anemia. She had signs and symptoms suggestive of renal failure and cerebral edema. She had had several tonic-clonic convulsive episodes. Examination on her last hospital admission showed unconsciousness, generalized edema, dilated pupils with "negative" fundi, questionable cardiomegaly, and a precordial systolic murmur of medium intensity. The liver was felt two fingersbreadth below the costal margin. At times she had a hypertension. Laboratory studies revealed a leukocyte count of 8,000 with 88 per cent neutrophils. Corrected sedimentation rate was 42 mm per hour. Urinalysis showed 4 plus albuminuria with frequent red and white blood cells. Blood urea nitrogen was 114 mg per 100 ml; sodium, 107 mEq per liter; potassium, 5.4 mEq per liter; CO_2 18 mEq per liter; chlorides, 42 mEq per liter; calcium, 3.2 mEq per liter; urinary sodium and chlorides, negative. X-ray showed increased bronchovascular markings. An electrocardiogram showed changes compatible with severe electrolyte disturbance.

*Capt. Harold H. Hoefle, Jr., USAF (MC), Medical Service.

In a 16-year-old girl with nausea and vomiting *without* edema, and with two and one-half months of amenorrhea, the possibility of pregnancy should be considered. However, since she had the diffuse bleeding episodes, one would think that she had miscarried if she had been pregnant.

Diagnoses of preeclampsia and eclampsia, though rather rare before 24 weeks, can be fairly well ruled out with the history of several profuse hemorrhagic episodes, even with the provision that pregnancy pre-existed.

Also, one must think of acute renal disease, particularly acute glomerulonephritis, in an individual of this age. The moderately acute onset of nausea, vomiting, and generalized edema would certainly suggest acute glomerulonephritis, but we do not know what the urine findings were from October to March. We could speculate that she went through an acute episode of glomerulonephritis and continued into a terminal stage. This is a good possibility with the later physical and laboratory findings of renal failure with proteinuria, hematuria, azotemia, and electrolyte imbalance. We do not know what the serum phosphorus was, but the serum calcium was severely depressed. Acute glomerulonephritis remains a distinct possibility.

Another thing which should be considered regarding renal disease is a type of nephrosis or nephrotic syndrome. Nephrotic syndrome does not include cells in the urine to the extent we have in this case, but there is some difference of opinion regarding this entity. She may have had a mixture of nephritic-nephrotic disease. There is no evidence that she had previous chronic renal disease or previous hypertensive disease.

Her course is one of a chronic nature in that it ran for five months before her admission in March 1953. During this time she was progressing neither favorably nor was she suffering any severe acute embarrassment. She had menorrhagia, but it was not a course that one might see in eclampsia if she were pregnant.

Let's think again along the line of chronic renal disease. I favor a collagen disease of the kidney, either disseminated lupus erythematosus or periarteritis nodosa, as the most likely diagnosis. Of these two possibilities I have attempted to compare and contrast the characteristics. The age at onset of lupus erythematosus is perhaps 15 to 40, versus 20 to 40 in periarteritis nodosa. Arthralgia and cutaneous lesions both are slightly more common in disseminated lupus erythematosus than in periarteritis nodosa. The patient demonstrates neither of these. Cardiovascular involvement is equally frequent. She has cardiovascular involvement. Hypertension is much more prevalent in periarteritis nodosa than in lupus. She has hypertension. Pulmonary lesions are equally divided. She has no pulmonary lesions except for increased bronchovascular markings. She has no pleurisy or effusion. Abdominal pain is more common in periarteritis nodosa; she does not complain of abdominal pain. Impairment of renal function

is more commonly found in periarteritis nodosa, which she certainly shows. Peripheral neuritis and splenic enlargement are not present. Focal cerebral lesions are more common in periarteritis nodosa. Muscular inflammations are equally divided, and she does not complain of this. As far as abnormal laboratory findings are concerned, anemia is slightly more common in lupus, although it is certainly found in both. The leukocyte count usually is elevated in periarteritis nodosa and usually depressed in lupus erythematosus. Her leukocyte count is neither depressed nor elevated. Eosinophilia is more common in periarteritis nodosa. No mention is made of an eosinophil count in the protocol. Abnormal urinary sediments are more common in lupus. LE preparation apparently was not done.

From these comparisons, I favor periarteritis nodosa. I do not believe she shows any features of other types of disease, with the exception of acute glomerulonephritis progressing to the terminal stage. I would diagnose this case as a type of renal insufficiency due to a collagen disease, particularly periarteritis nodosa, with the outside possibility of disseminated lupus erythematosus. Also, one must consider acute glomerulonephritis which goes into a terminal stage.

Doctor Jernigan:* You conclude, therefore, that she died from renal insufficiency primarily with periarteritis nodosa the first diagnosis, followed in order of probability by disseminated lupus erythematosus and acute glomerulonephritis?

Doctor Hoefle: Yes.

Doctor Jernigan: Dr. Abrams,** I would like to ask you to comment on the electrolyte imbalance. The electrolyte findings are unusual even for severe renal insufficiency. After she was admitted to the service hospital, the blood urea nitrogen was 152 mg per 100 ml; the potassium was 3.6 mEq per liter; sodium, 112 mEq per liter; and the chlorides were reported as 69 mEq per liter. Also, for the degree of insufficiency, the CO_2 was only 17.7 mEq per liter. How do you explain the low potassium if we assume that this is an accurate report?

Doctor Abrams: The presence of the low potassium is difficult to explain. There are two possibilities: (1) The patient is storing some potassium; and (2) she is losing potassium, just as she is losing salt. Of course, the mechanism in the loss of salt is quite different from that in the loss of potassium, and one of the things that causes an excessive loss of potassium is an elaboration of a larger than normal amount of aldosterone. The entire electrolyte imbalance is very confusing to me. I have been unable to explain it logically. The 3.2 mEq per liter of calcium initially and later reported as 2.9 and 3.6 mEq per liter is very striking. Of course, low calcium is found in extensive

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**Maurice J. Abrams, M. D., Civilian Consultant in Internal Medicine.

renal damage, but the use of large amounts of citrate can also cause low calcium. The 15 transfusions, probably of citrated blood, although some of them were previously given, might possibly have been instrumental in initiating that degree of hypocalcemia. Another thing is that many people believe that where there is a so-called "salt-losing nephritis," the salt is not lost but is actually stored, primarily in bone and cartilage. I do not know whether in those individuals there is more of a calcium aberration in the electrolyte figures than one usually sees in kidney failure.

Doctor Jernigan: Unfortunately, the potassium output in the urine was not reported. At one time, though, there was no sodium or chloride in the urine.

Doctor Abrams: This sounds like a type of "low-salt syndrome," where there is no salt loss, but there is an expansion of the total volume of fluids and a storage of sodium and chloride in the bones, cartilage, et cetera.

She had not been on restricted sodium intake and she had not been given diuretics. She had the possibility of plasma expansion, but I do not think sufficient to explain the vast changes that are recorded. I think that in this case these electrolyte findings are the result of renal impairment. On the available data I would go along with Doctor Hoefle for a diagnosis of periarteritis nodosa as a basis for the extensive renal damage.

Doctor Jernigan: Thank you, Doctor Abrams. Doctor McGettigan,* this girl was 16 years old and she had been married two and one-half months. During her marriage she had not menstruated and then she developed nausea, vomiting, and generalized edema. A month later she began to have vaginal bleeding and subsequently more bleeding and renal failure. What do you think about the possibilities of this being a complication of pregnancy or complications of attempted modification of the pregnancy?

Doctor McGettigan: Of course, that could very well exist. Just getting married could have made her amenorrheic. However, I think this is more a reflection of some other basic disease rather than the primary gynecologic problem. Since we do not know what the findings were early in the illness, I do not think you could say categorically that it was not a primary gynecologic abnormality. In girls who have abortions, infections are usually severe and they may get a renal shutdown, but they do not have the hemorrhagic manifestations that this girl had. I do not think that Doctor Morrissey will reveal significant disease in the uterus.

Doctor Jernigan: Her uterus was packed for hemostasis. Do you usually do a D & C prior to the packing, Doctor McGettigan?

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*Maj. Manus J. McGettigan, USAF (MC), Chief of Obstetrics and Gynecology.

Doctor McGettigan: Yes. You would be interested in knowing the type of uterus she had, and you might get valuable information from doing a D & C.

Doctor Jernigan: If she had had an abortion, would it be possible to make the diagnosis?

Doctor McGettigan: Yes, you could probably find some elements of conception remaining. She could well have been pregnant, and this picture could be seen in a patient with complete abortion; however, they usually do not have this extensive bleeding. Of course, one usually does something about the bleeding before. Apparently they waited a month and did nothing about it.

Doctor Jernigan: Do you think, Doctor Baird, that we should entertain the possibility of a renal poison such as arsenic or mercury?

Doctor Baird: I do not think the history is good for heavy metal toxicity. First, there is quite a severe gastritis and gastroenteritis, then the next organ attacked is the kidney. I think the tubules are probably the hardest hit. The course is usually rapidly downhill and if the kidney does recover, the recovery is usually more prompt than this. However, in some cases the course may be long and the recovery may not be complete. I do not think that mercury poisoning is very likely in this case.

Doctor Jernigan: Do you think the same holds true for arsenic poisoning?

Doctor Baird: Arsenic poisoning is a rather difficult subject to talk about. Usually the ingestion of large amounts of arsenic is rapidly fatal. Most cases of ingestion have been over a long period of time in small amounts. This causes central nervous system symptoms and other rather bizarre symptoms. I do not think arsenic poisoning is a very good possibility.

Doctor Nunnally:* Would bilateral cortical necrosis from a hematologic crisis result in a slow downhill course of renal insufficiency?

Doctor Baird: I suppose it could. In several reported cases there was a marked hematuria and toxicity with a more rapid downhill course than this patient showed.

I would disagree with one statement by Doctor Hoefle. I believe the renal lesions are more common in lupus than in periarteritis nodosa. In the terminal stage of lupus, renal disease is present in over 90 per cent of these cases. Of course, it depends on the stage and the severity of involvement as to whether or not this is a prominent feature.

I believe this case is best explained by a diagnosis of acute renal tubular damage from shock.

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*Capt. Richard M. Nunnally, USAF (MC), Laboratory Service.

Doctor Hoefle: Is it possible that the patient had adrenal cortical involvement?

Doctor Abrams: With hypertension present, adrenal insufficiency is most unlikely.

Doctor McGettigan: Could not this be well explained by a very severe hemorrhagic crisis and anemia, plus the insults from local treatment of the bleeding uterus and the possibility of a transfusion reaction?

Doctor Jernigan: That is a very good suggestion, and the time intervals are compatible with this mechanism of renal failure. But the blood urea nitrogen was only up to the 50's by March, which was some six months after she began to bleed and receive most of the transfusions. We are not aware of an overt hemolytic crisis, but sometimes the delayed type of blood reaction causes severe renal damage.

Doctor Morrissey, we all agree that this girl died from renal insufficiency. Most of the doctors favor collagen disease as the cause. Doctors Abrams and Hoefle place periarteritis nodosa at the top of the list. I will suggest acute glomerulonephritis as more likely. Doctor Baird's diagnosis is acute renal tubular failure from shock. A delayed transfusion reaction was mentioned by Doctor McGettigan.

Doctor Hoefle's diagnoses:

1. Periarteritis nodosa
2. Acute glomerulonephritis
3. Disseminated lupus erythematosus

PATHOLOGIC FINDINGS

Doctor Morrissey: The autopsy findings were those of subacute glomerulonephritis. In addition, there was a secondary cryptococcosis of the lungs, which is demonstrated in figure 1. There was no extension in this case to the central nervous system.

The kidneys were large and pale. The cortex was cloudy and granular. Microscopically the glomeruli showed epithelial proliferation, obliteration of Bowman's space, and some endothelial proliferation. There was an occasional hyalinized glomerulus. Tubular degeneration and atrophy were present. Only a slight interstitial infiltration was seen. The blood vessels showed slight to moderate changes (fig. 2).

Glomerular nephritis is a disease which attacks the glomeruli and the tubules. The primary changes are inflammation in the glomeruli, with secondary changes in the tubules, interstitial tissue, and blood vessels. The glomerular changes consist of endothelial proliferation and swelling, epithelial proliferation, thickening of basement membrane, intercapillary fibrosis, and intercapillary exudate of leukocytes, serum, and fibrin. These changes cause an obliteration of the glomerular capillaries and result in decreased blood flow and urine filtration. The tubules atrophy if the glomeruli fail, or hypertrophy if the glomeruli persist. This causes a slight shrinkage in the substance of the kidneys.

Subacute glomerulonephritis sometimes occurs as a sequela to typical acute glomerulonephritis while at other times it is a primary disease in itself.

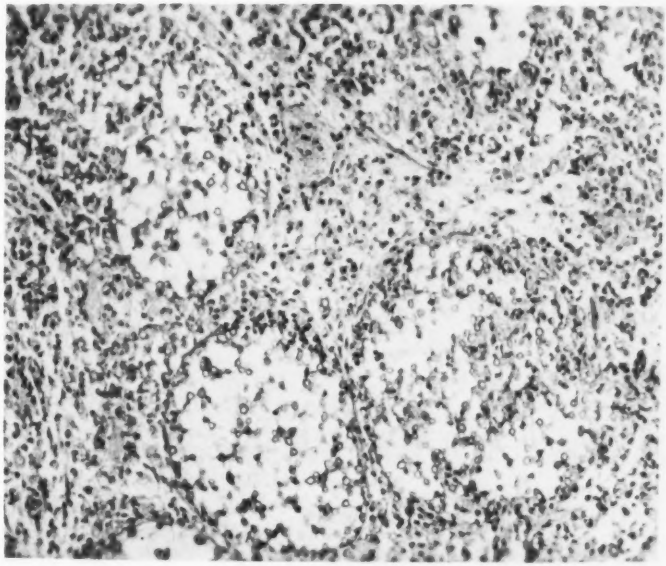

Figure 1. Cryptococci in the lung. (× 260)

The clinical findings are usually marked edema and proteinuria. Four factors are responsible for the edema: (1) Decreased urine formation; (2) increased capillary permeability from loss of protein and a basic capillary defect; (3) elevation of hydrostatic pressure by heart failure; and (4) increased resorption of sodium and water by tubules. The blood pressure in subacute glomerular nephritis is variable. Some have no rise, 25 per cent have a transient rise, and in approximately 10 per cent it reaches levels around 180 to 200. The cerebral manifestations follow the blood pressure rise and are not usually associated with the nitrogen retention. Cerebral ischemia due to arteriolar spasm and hypertension quite often results in cerebral edema. Death not uncommonly follows convulsions. The urine volume may not change throughout the disease, while in other cases it may decrease. In 5 per cent complete anuria has been reported.

The incidence of subacute glomerulonephritis shows a sex predominance, occurring in males twice as often as in females. Most cases occur before 40 years of age. Exposure to cold and familial factors have no demonstrable effect. The cause is obscure but the disease frequently follows acute glomerulonephritis. Thus, a streptococcal infection may be an etiological factor.

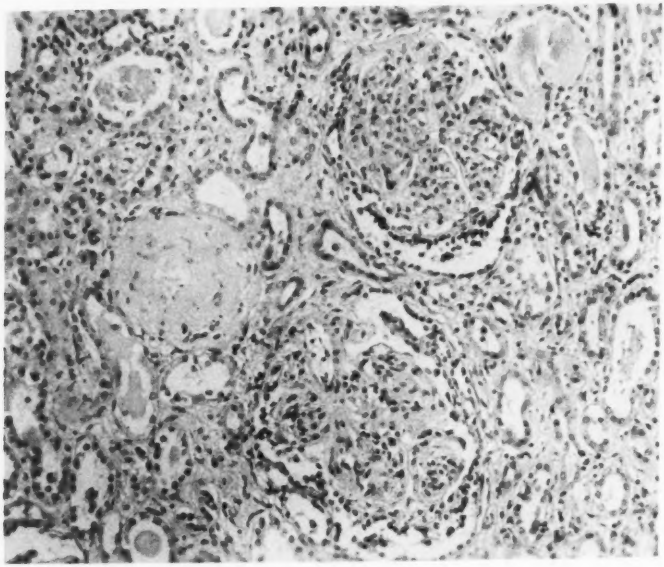

Figure 2. Photomicrograph of kidney showing changes in glomeruli, tubules, and interstitial tissue. (× 200)

Pathologic diagnoses:

1. Subacute glomerulonephritis, the primary cause of death.
2. Cryptococcus of the lungs, an incidental finding.

There were no other remarkable findings.

Mediastinal Mass Simulated by Caval Phlebectasia

BYRON G. BROGDON, *Captain, USAF (MC)*
NEIL E. CROW, *Captain, USAF (MC)*

THE finding of an unsuspected mediastinal mass during routine roentgenographic examination of the chest poses a difficult problem often requiring extensive study for accurate diagnosis and intelligent handling.

Such a mediastinal mass of most unusual origin is described in the following case report.

CASE REPORT

A 22-year-old airman incurred a severe contusion to the anterior chest wall and multiple fracture-dislocations of the right tarsometatarsal region in an aircraft accident on 15 July 1956. There was severe chest and back pain with respiration and a mild hemoptysis. A roentgenogram of the chest at that time (fig. 1) was reported as showing "marked congestion of the lung fields, probably due to intrapulmonary hemorrhage." The rib cage was intact.

Chest symptoms cleared rapidly, as did the lung fields on subsequent radiographic examination. During the next 12 months, the patient received extensive orthopedic treatment. Upon termination of his enlistment, he was referred to this hospital, 26 July 1957, for disposition.

On admission, the patient was asymptomatic except for orthopedic disability. Exclusive of this disability, physical examination findings were within normal limits. Routine laboratory findings were normal.

A routine roentgenogram of the chest on admission revealed a smooth widening of the superior mediastinal shadow on the right (fig. 2). Differential diagnoses considered included aneurysm of the ascending aorta, persistent right aortic arch (double arch), mediastinal adenopathy, or mediastinal mass of other origin. An extensive chest work-up was undertaken.

Review of the immediate post-injury chest film (fig. 1) revealed that in addition to the pulmonary findings reported, there was a widening of the right superior mediastinal shadow at that time.

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Cardiac fluoroscopy showed the mediastinal mass in question to pulsate. These pulsations were thought by the fluoroscopist to be transmitted rather than expansile in type. The examination was otherwise essentially noncontributory.

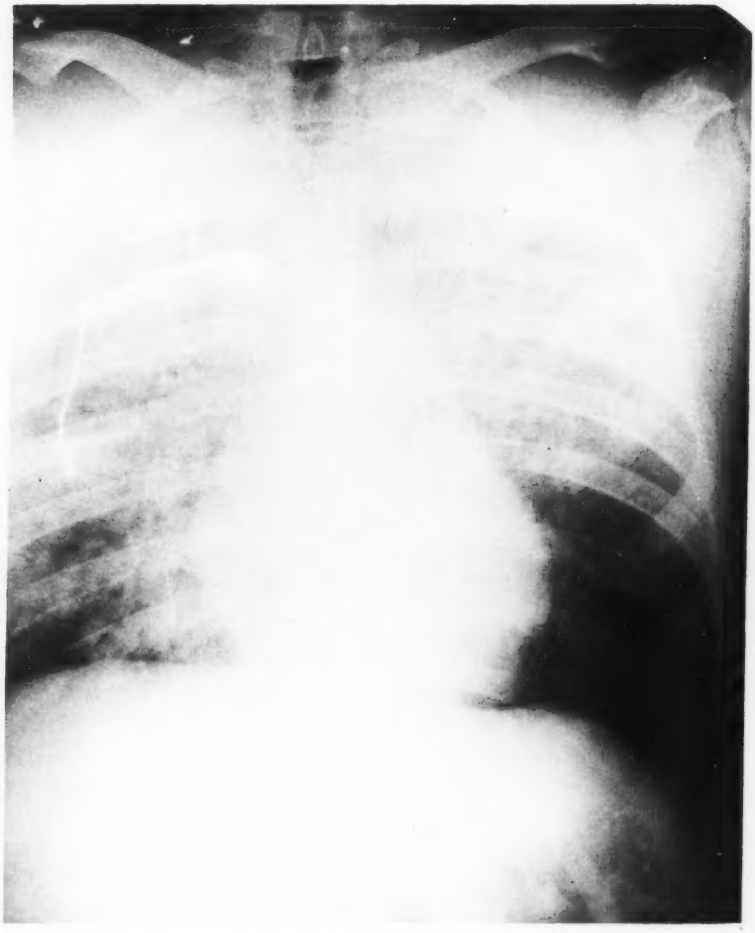

Figure 1. Roentgenogram immediately after aircraft accident, 15 July 1956, showing diffuse densities throughout both lung fields and widening of the superior mediastinal shadow on the right.

An angiocardiogram through the left antecubital vein (fig. 3) revealed the mass to be a dilated superior vena cava. The left and right innominate, left subclavian, and left axillary veins were similarly widened. There was a suggestion of some narrowing of the superior

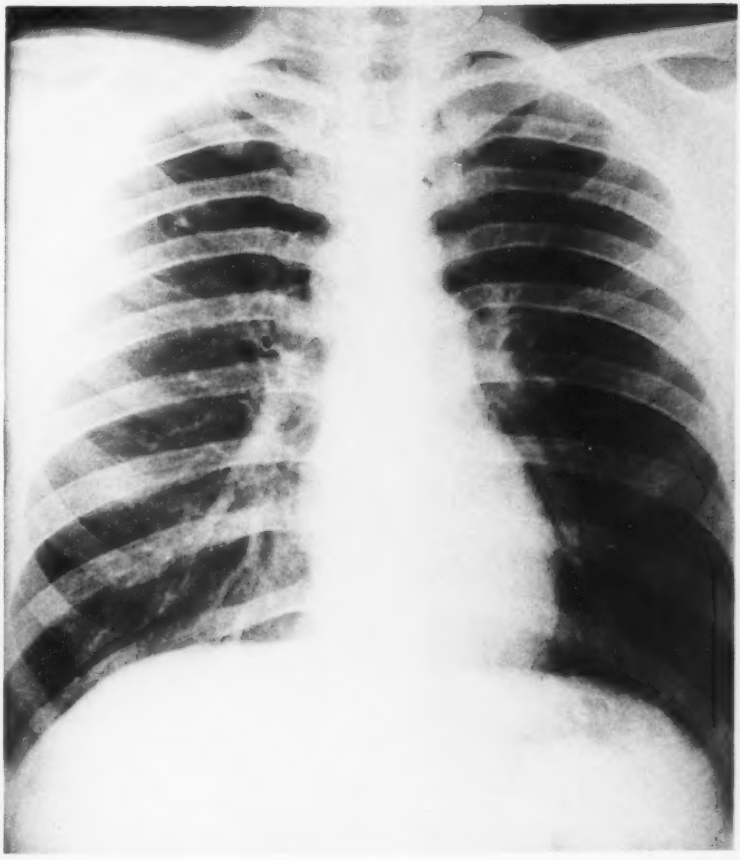

Figure 2. Roentgenogram on 26 July 1957, showing widening of the superior mediastinal shadow on the right.

vena cava central to the dilatation. No other vascular or cardiac abnormalities were demonstrated.

Venous pressure, arm-to-tongue, and arm-to-lung circulation times were normal.

Cardiac catheterization via the left antecubital vein disclosed normal pressures and oxygen saturation in the superior vena cava, inferior vena cava, pulmonary artery, right atrium, and right ventricle. There was no evidence of caval obstruction or of cardiovascular anomaly.

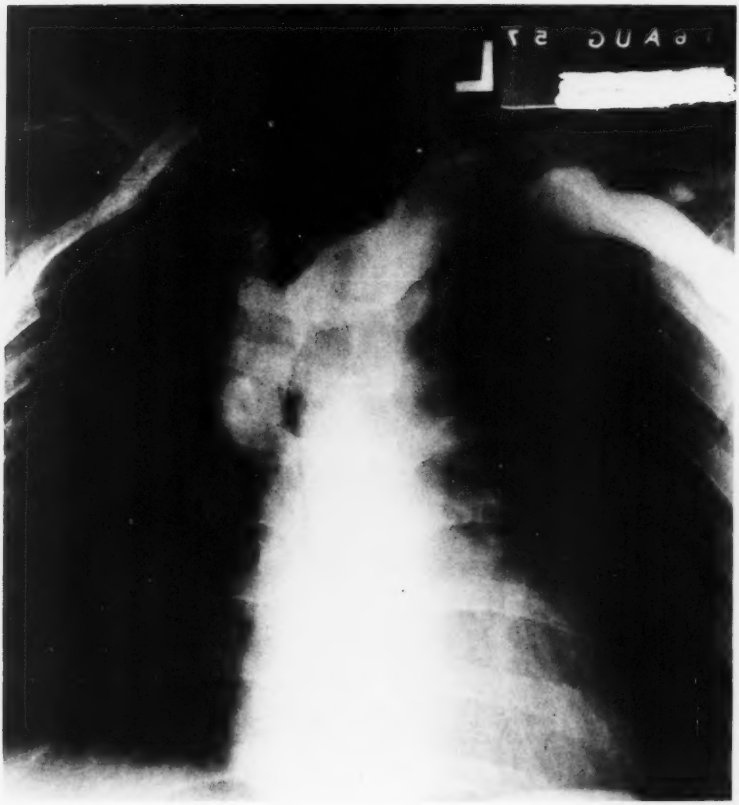

Figure 3. Angiocardiogram showing dilatation of the superior vena cava, both innominate veins, left subclavian veins, and left axillary vein.

Subsequently, mass survey photoroentgenograms of the chest taken in 1951 and 1952 were obtained (fig. 4). These showed no change in over-all appearance or in the right superior mediastinum when compared with the current studies.

The final diagnosis was idiopathic dilatation of the superior vena cava and feeding veins, probably congenital.

DISCUSSION

The normal superior vena cava is variable in size, ranging from 4.2 to 12.0 cm in length and from 8.0 to 20.0 mm in diameter. The mean diameter and length for 150 patients with no evidence

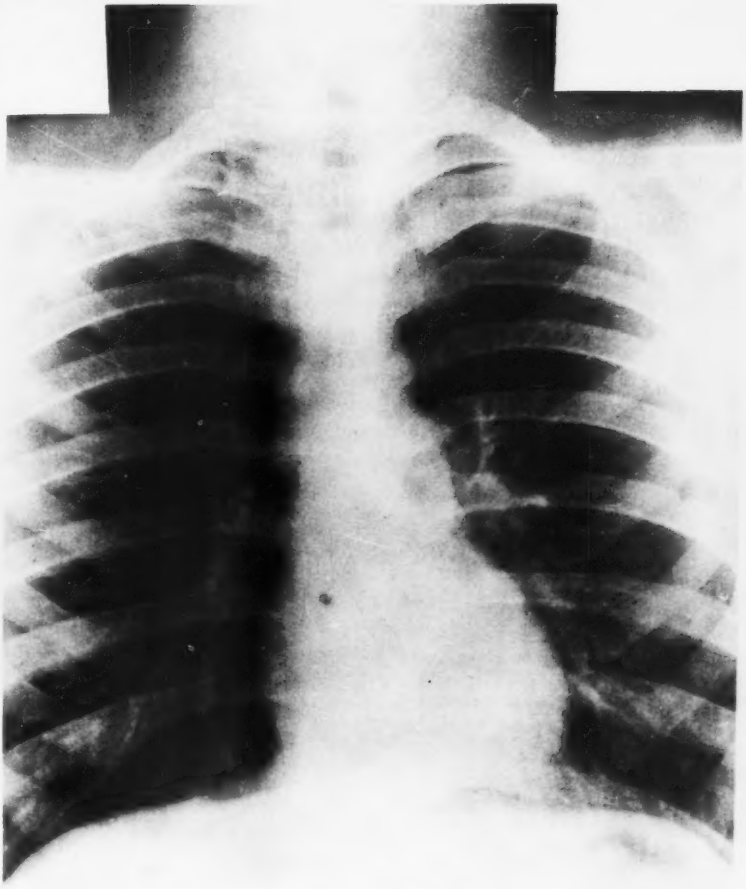

Figure 4. Photoroentgenogram on 19 February 1952, showing widening of the superior mediastinal shadow on the right, present at that time.

of abnormality was 14.8 mm and 7.7 cm respectively. The innominate veins show a similar variation.[1]

Dilatation of the superior vena cava and its tributaries has been related to saccular aneurysm of the superior vena cava, obstruction of the superior vena cava near the right atrium, right-sided heart failure, pericardial effusion, constrictive pericarditis, tricuspid insufficiency, and congenital cardiovascular anomalies producing increased pressure or flow within the vessel.[1-4] These

lesions, upon thorough study, will present characteristic findings which were not present in our case.

On plain film and angiocardiographic studies, Abbott's[5] case of aneurysm of the superior vena cava somewhat resembles the case reported here. Careful comparison of the two cases, however, reveals a number of dissimilarities.

The complete absence of any significant findings associated with or related to the venous dilatation led us to the diagnosis of idiopathic phlebectasia. Because of the diffuse nature of the abnormality and the lack of change over a long period of observation, thoracotomy was thought unwarranted.

This lesion is undoubtedly a most uncommon cause of mediastinal mass. It is thought, however, that the case reported is of interest as an unusual abnormality. Furthermore, it reemphasizes the necessity for employment of every available diagnostic facility in the study of mediastinal problems prior to thoracotomy.

ACKNOWLEDGMENT: The authors wish to thank Doctor H. Corwin Hinshaw, who initially suggested that this case be reported.

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Sulfapyridine in Dermatitis Herpetiformis

Report of a Case Under 11 Years of Continuous Treatment

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SULFAPYRIDINE was first used in this country in 1938 in the treatment of pneumococcal pneumonia, for which it already had been found effective in England. In April of 1939 Costello[1] reported success with sulfapyridine in the treatment of a case of dermatitis herpetiformis (Duhring's disease) that had not responded to sulfanilamide or other medications over a four-year period. His patient presented marked improvement in one week, with complete clearing after two weeks of therapy, but a maintenance dose was required. After eight months of administering one half tablet every other day the patient remained clear.

Barling[2] later reported that one of his patients who had been started on sulfapyridine in 1939 for acute tonsillitis also had noted a great improvement in his dermatitis herpetiformis, and had been maintained successfully on the drug for a four-year period. During this span, he was able on occasion to dispense with sulfapyridine and remained clear of his dermatitis for a 3 to 4 week period, after which time his skin would again erupt. Eventually he was maintained on one gram every 48 to 96 hours and would be relieved within 2 to 3 hours after reinstitution of therapy.

Senear and Perlstein[3] were able to demonstrate repeatedly the efficacy of sulfapyridine in a five-year-old patient through deliberate cessations and reinstitutions of therapy, with equally good results each time the drug was resumed. Brunsting[4] reported clearing in a 30-year-old patient after one week of therapy. His patient had been treated unsuccessfully for a 20-year period with other medications. As in other cases, a maintenance dose was necessary.

In 1943 Swartz and Lever[5] compared the effect of sulfapyridine to that of sulfanilamide, which previously had been found effective by Lain and Lamb.[6] The comparative study of 13 patients revealed both drugs to be effective, with sulfapyridine more effective and in smaller doses. All of the 13 patients

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were benefited, pruritus being considerably relieved within 12 hours, and good improvement being noted 2 to 3 days after therapy was begun. Additional studies revealed that sulfathiazole had some beneficial effect, whereas sulfadiazine and sulfaguanidine had none. More recently Everall[7] reported on 17 patients, 15 of whom he had maintained on an average dose of one and one half grams daily. Only one of these had failed to respond well.

Although it has been a general consensus that sulfapyridine is a good therapeutic agent in the treatment of dermatitis herpetiformis, there are patients who cannot tolerate the drug because of side effects. These vary from slight nausea to agranulocytosis. Most commonly, the patient will complain of nausea, malaise, vertigo, or mental depression. Drug eruptions[8] may develop. Molesworth[9] was able to lower the dosage of sulfapyridine and maintain good results in 6 patients who could not otherwise tolerate the drug, by giving folic acid, 10 to 20 milligrams daily. He suggested that folic-acid deficiency could be an important factor in causing toxic symptoms.

In patients who cannot tolerate sulfapyridine or who do not respond well to this drug, the sulfones often prove beneficial. Promacetin (brand of acetosulfone),[10] Diasone Sodium (brand of sulfoxone sodium),[11] and the parent compound diaminodiphenylsulfone[12] have been used successfully. With use of the sulfones or of sulfapyridine, regular and frequent blood studies and urinalyses are indicated.

CASE REPORT

A 56-year-old woman, with a five-month history of an itching, crusting eruption that began on the arms and legs and after 2 to 3 weeks became generalized, was first seen in the private practice of Doctor Rudolf L. Baer in 1946. During the preceding five months, she had received autoblood injections, roentgen-ray treatments, various hormones, and arsenic and other internal medications, without improvement. On examination, there were found up to palm-sized patches of grouped, excoriated, papulovesicular lesions, widely distributed over the entire body except for the face, neck, hands, feet and genitalia. Some hyperpigmentation was present in the subsiding and healed areas. There were coin-shaped eczematous plaques on the medial surface of one ankle.

In April 1946 the patient was given sulfapyridine three grams daily with sodium bicarbonate by mouth, and a lotion containing menthol, phenol, crude coal tar, and sulfur for topical treatment. Within one week her eruption was about 80 per cent improved. She had much less pruritus and had developed no new lesions. The sulfapyridine was reduced to two grams daily, but three days later, because of pruritus, was increased to three grams daily. This brought relief after three days, at which time the patient noticed some fatigue.

Sulfapyridine was maintained at three grams daily until July, when it had to be discontinued because of a neutropenia. Seven days later, because of increased pruritus, the patient was again placed on two grams daily, with only slight improvement until she was given three grams daily. During the following 18 months she was maintained on two to three grams daily, as needed for relief. On one occasion during this interval, when the dosage was temporarily lowered to one and one half grams, the eruption became more pronounced and spread to previously involved areas.

In February 1949 the patient was given a total of three injections at weekly intervals of Flo-Cillin (brand of crystalline procaine penicillin G), receiving 297 grams (300,000 units) of penicillin at each injection. The penicillin was discontinued because of an intensely pruritic morbilliform eruption, without any effect being noted on the original eruption.

During the following 20 months, the patient was maintained adequately on one to two grams of sulfapyridine daily. The only episode of increased pruritus during this interval occurred after gradually reducing the dosage and discontinuing it entirely for one week. Several days after reverting to three grams of sulfapyridine daily, the symptoms were relieved.

In October 1951 internal medication was discontinued again, but was resumed after seven days because of increased pruritus. From January 1953 until July 1955, adequate control was obtained on one half gram daily, but later in 1955 the dose was increased to one gram daily because of some crusting of the scalp that failed to clear on the lower dose.

The patient has been observed at intervals since then and was last seen in June 1957, while on one half gram daily. She is doing well, but states that if she neglects taking a single tablet, pruritus develops within 24 hours. The only other internal medication which the patient takes is one tablet of pyribenzamine daily. Regular blood studies have shown no toxic effects since 1946, during the third month of medication, when the sulfonamide had to be temporarily discontinued.

COMMENTS

During the entire period of observation, this patient has had an eosinophilia. This was 6 per cent of the total white blood cell count at the time she was first seen, whereas subsequent blood examinations have shown as high as 27 per cent. There has been no apparent relationship of the degree of eosinophilia to the dosage of sulfapyridine. The neutropenia that became evident during the third month of medication while on 3 grams of sulfapyridine daily has not been manifest since, although comparable doses have been given for short periods.

The response of dermatitis herpetiformis to sulfapyridine is difficult to interpret, as neither the mechanism of action in this disease nor the etiology of the disease are known. It is unlikely that an antibacterial action against the disease itself, or against a focus of infection, could offer a satisfactory explanation, considering that dosage as small as one half gram daily may be sufficient to control symptoms and clinical manifestations over prolonged periods.

SUMMARY

A patient with dermatitis herpetiformis has been maintained on sulfapyridine for 11 years with complete control of all symptoms and clinical manifestations. Side effects have been minimal and there are no demonstrable ill effects from the prolonged medication.

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Alkaptonuria

DAVID MARSHALL, *Captain, USAF (MC)*

ALKAPTONURIA is a disorder of protein metabolism characterized by the excretion in the urine of large amounts of homogentisic acid, an intermediary substance of tyrosine metabolism. Presumably the body lacks a specific enzyme or enzyme system for the catabolism of homogentisic acid. This defect is thought to be hereditary, inasmuch as there is a definite familial tendency to this disease.

The entity of alkaptonuria attracts the attention of the clinician because of its rare occurrence and the dearth of existing information about this disease. Only slightly over 200 cases have been reported in the literature, and the disease is rarely encountered, even in a general hospital.[1] Consequently, it is believed that the occurrence of another case should be noted in the literature, and the fact that this case was seen at a U. S. Air Force Dispensary points up the importance of keeping this entity in mind wherever medicine is practiced.

CASE REPORT

A 32-year-old aeromedical specialist at this facility reported for an annual physical examination, and in the course of this, submitted a urine specimen. The laboratory was busy and the specimen was left overnight, only to be found colored black in the morning. The possibility of alkaptonuria was entertained and analysis of the pint specimen revealed 20 mg percentage of homogentisic acid.

The past history and review of the systems was unremarkable and the patient was in good health. There had been no complaints of arthritis or other symptoms. The general physical examination revealed no abnormalities. There was no evidence of pigmentation of the scleras, cartilages of the ear, or other parts of the body.

A complete blood count, urinalysis, chest and lumbosacral spine films, and serology test were all within normal limits, and all previous urinalyses were reviewed and found to be negative.

The patient's family, consisting of one brother, two sisters, and parents, were queried in correspondence, and none of their urine specimens was observed to turn black or brown after standing for 24 hours.

From U. S. Air Force Dispensary, Charleston Air Force Base, S. C.

DISCUSSION

Tests for Detection of Homogentisic Acid in Urine

Most of the tests described are nonspecific and several are reported as giving a false negative result. The most reliable test, of course, is the determination by isolation. Chromatography, which is a simpler procedure than isolation, is probably more feasible and next most reliable.[2] The remainder of the tests described give varying results and all were negative in this case except for the oxidation test.

Oxidation test. The urine turns dark on standing. This occurs supposedly because homogentisic acid polymerizes during the process of oxidation, becoming a black or brown-black pigment. It should be pointed out that porphyrin, melanin, and possibly phenolic compounds can give a dark urine on standing and should be ruled out.

Sodium hydroxide test. An alkaline urine hastens the process of oxidation and, therefore, this is an elaboration of the oxidation test.

Benedict's test. Homogentisic acid causes a reduction of copper salts in alkaline solution.

Ferric chloride test. The addition of a few drops of ferric chloride produces a transient blue color.

A drop of alkaline urine placed on a sensitized photographic paper causes the immediate appearance of a black spot on the paper.

Other tests, which are nonspecific, have been described in the literature.

This relatively asymptomatic disease usually is noted in childhood when diapers or undergarments frequently stain black.[3,4] It is stated that approximately 50 per cent of all patients with alkaptonuria go on to develop ochronosis—an entity characterized by the deposition of pigment in the cartilaginous areas, most commonly the joints, and giving rise to the symptoms of arthritis. This occurs most frequently in the third or fourth decade and most commonly involves the joints of the spine. The exact nature of the pigment is unknown, though it is believed to be formed from homogentisic acid. Except for this complication, alkaptonuria is a benign disease with no effect on longevity.

An important and confusing effect of the disease is its ability to cause a false positive test for glucose in the urine by reducing Benedict's solution. Consequently, the development of an atypical or black precipitate when doing a Benedict's test should make

one think of this disease. In addition, a patient in the third or fourth decade who complains of arthritic symptoms also should alert the clinician to rule out ochronosis by testing the urine for the presence or absence of homogentisic acid.

There is no known treatment for alkaptonuria. The disorder has been produced in some normal humans and in experimental guinea pigs by feeding them a diet deficient in vitamin C, accompanied by oral doses of tyrosine. When vitamin C then was supplied the homogentisic acid disappeared from the urine. However, to the author's knowledge, no clinical case of alkaptonuria has been affected by the administration of vitamin C.[5] Cortisone has been used orally in an effort to alter the basic metabolic defect with no change in the urinary output of homogentisic acid in an alkaptonuric; however, one patient with ochronosis did develop a decrease in the urinary output of pigment on cortisone, accompanied by relief of arthritic symptoms, with recurrence of symptoms when cortisone was discontinued.[6]

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DR. BERRY HONORS TURKISH HERO IN ANKARA, GIVEN MEDAL OF HONOR IN PARIS CEREMONY

Dr. Frank B. Berry, Assistant Secretary of Defense, (Health and Medical), and Major General Tevfik Guner, Surgeon General of the Turkish Armed Forces (above) led a delegation of civilian and military physicians in Ankara to place a wreath on the tomb of Ataturk, first president of the Turkish Republic, during the second Armed Forces International Conference on Nutrition 14, 15, and 16 April 1958.

Below, Dr. Berry (second from left) is shown wearing the French Army's *Médaille d'Honneur du Service de Sante en Or* awarded to him at a banquet in his honor at Val de Grace Hospital in Paris by Major General Alfred Reilinger (left), Inspector General of the French Military Medical Services. To the right of Dr. Berry, are Major General Raymond Debenedetti, Surgeon General of French Armed Forces, Major General William H. Powell, Jr., USAF (MC), Chief Medical Officer of SHAPE, and Dr. J. P. Beyne, president of the Association of Military Surgeons of France. Usually awarded posthumously, Dr. Berry received the medal for his aid to the Free French Army in World War II. It has been given to living persons on only three previous occasions.

ADMIRAL HOGAN TOURS NAPLES, MEETS PETE

During a recent tour of U. S. Navy medical facilities in Naples, Rear Admiral Bartholomew W. Hogan, Surgeon General of the Navy, met "Pete," a white leghorn rooster, whose blood is used in testing Mediterranean area influenza strains at the Navy's Preventive Medicine Unit No. 7. Shown above, from left to right, are Captain Van C. Tipton, MC, USN, officer-in-charge of the unit, Admiral Hogan, Hospital Corpsman, first class, W. J. Steeger, and Pete.

Annual Anesthesiology Meeting, 7-12 July

The fifth annual Anesthesiology Review Session of the Armed Forces will be held at the U. S. Air Force Hospital, Lackland Air Force Base, Tex., 7-12 July 1958. The instructors' panel for the meeting includes John Abajian, Jr., M. D., University of Vermont College of Medicine; Charles R. Allen, M. D., University of Texas School of Medicine; Raymond F. Courtin, M. D., Baylor University Hospital, Dallas, Tex.; George W. N. Eggers, M. D., University of Texas School of Medicine; and Major Joseph T. Melton, USAF (MC), Lackland Air Force Hospital, under the presidency of Brigadier General Robert E. Lee, USAF (MC), Surgeon, Tactical Air Command. The society was organized in May 1957 to foster the advancement of the art and science of surgery in the Air Force and to encourage clinical and laboratory investigation of various problems of surgical significance.

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A MESSAGE FROM THE A. M. A.

The article this month will consider the problems of that rapidly growing population group in the United States, our senior citizens. The aged population of the United States has increased by over 11,500,000 persons since the turn of the century. In 1900 there were 3,080,000 persons 65 years of age and over. It is estimated that there now are 15,000,000 persons in this age group. While the population as a whole doubled during this period, the number 65 years and over has quadrupled. By 1975, it is estimated that there will be 21,000,000 to 23,000,000 persons in this group, but as a per cent of total population it is leveling off at about 9 to 10 per cent.

However, as the size of the older age groups increases in over-all numbers, the problems which confront older persons assume more importance for those directly and indirectly affected. New problems that occur in the health, emotional, social, economic, and psychologic areas of the lives of all persons are intensified in the older person. While other age groups in the population have the flexibility to rebound from some of these problems, the aged must adjust to a series of limitations that have arisen in the past decade or two. The aged person must learn to accept his physical and mental disabilities or limitations; to face possible retirement due to inflexible retirement policies although he is able to carry on his work adequately; to face the loss of prestige and satisfaction of a job accomplished well, a decrease in social participation, the continuing loss of his relatives and contemporaries, and change in his mode of living brought about by persons and possibly himself thinking he is "old" and therefore of little use.

Even though this is a growing mass problem of some 15,000,000 individuals, the significant factor lies in how a person adjusts to this change of his style of living. His ability to adjust is based on his emotional and psychologic background. Students of mental change in the aged believe that the basic patterns of response in older persons remain essentially the same as their reactions to the stresses and frustrations of life in their working days.

These individual adjustments to change must be accomplished as quickly and as smoothly as possible. Although these individual problems must be answered when we consider the problems of the aged en masse, we are confronted with vaguely discerned out-

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From the Council on National Defense of the American Medical Association. The views and opinions expressed are not necessarily those of the Department of Defense. —*Editor*

lines of their social, psychologic, and economic status due to the increase of numbers in the last two decades. It would appear that everyone with an aged parent or relative is an "expert" on the aged. But the aged is not a static group, it is one of the fastest growing population groups, and while numerous research projects have been carried out on the problems of the older person, these surveys were normally made of a population that existed in the Great Depression of the 1930's or closely following the controlled economy of the war period. These surveys produced answers that are almost too pat; namely, old people are lonely; they must adjust to widowhood; they must live on reduced income; they suffer from a feeling of uselessness; they no longer have a role in society as a worker or a homemaker; and they are subject to increasing infirmity and disability.

We tend to accept without analysis. When the aged were a less significant number in our population, attention was placed by the medical profession on meeting the prime problems of medical care; that is, taking care of the growing family with provision of care for the child, the maternity case, and the acute episode. Such a policy was followed in the construction of most general hospitals. Such a policy was followed by the voluntary health insurance industry. Concentration was on taking care of the *main* medical problems. Now, that huge strides have been taken, the medical profession has been able to concentrate more research time and energy on the multiplying problems of the aged and other growing population groups.

Always interested in the problems of the aged, the American Medical Association had established a Committee on Aging as one of the committees of its Council on Medical Service. In the last two years much of the existing information on the sociomedical problems of the aged has been gathered. A series of regional meetings has been held to acquaint the physicians with the newest trends among the aged. In part on the basis of this work, to prevent any additional growth in problems of the aged, four medical organizations—the American Dental Association, the American Hospital Association, the American Nursing Homes Association, and the American Medical Association—have banded together to improve the health care of the aged. These organizations initially wish to find the answer to two main questions: In an era of improved surgery, tranquilizers, and finer hospitals and facilities, what are the sociomedical problems of the aged? And, what has happened since health surveys were made in the 1930's? Once we have a clearer understanding of the medical needs and the demands of the aged, we can urge proper policy to meet such needs. Simply to rely on small out-of-date samples will not lead to meaningful aid to the aged.

OFFICERS CERTIFIED BY SPECIALTY BOARDS

Supplementary Listing

The Surgeons General of the military medical services have announced that the following regular Medical and Dental Corps officers have been certified by the boards indicated since the listings published in previous issues of the *Journal*.

American Board of Pediatrics

Howard H. Johnson, Jr., Capt., USAF
Joseph G. Rossi, Lt., USN

American Board of Psychiatry and Neurology

Psychiatry

Charles E. Herlihy, Lt. Comdr., USN

Neurology

Theodore M. Badgley, Maj., USA

American Board of Orthopaedic Surgery

James T. Leslie, Jr., Maj., USAF
John F. Tracey, Maj., USAF
Roger A. Standard, Capt., USN

American Board of Dermatology

Henry T. Ash, Comdr., USN
William G. Lawson, Capt., USN
Everett P. Kirch, Capt., USN

American Board of Urology

Albin A. Galuszka, Capt., USN
Jack R. Robison, Maj., USAF

American Board of Internal Medicine

Orville F. Nielson, Comdr., USN
George H. Tarr, Capt., USN

Gastroenterology

James T. Hardy, Lt. Col., USAF
Emmett L. Kehoe, Col., USA

American Board of Pathology

J. Thornton Boswell, Lt. Comdr., USN
Francis J. McMahon, Capt., USN
John F. McCabe, Capt., USN

American Board of Ophthalmology

John E. Gill, Lt. Comdr., USN

American Board of Otolaryngology

Francis J. Sweeney, Lt., USN

American Board of Surgery

Homer S. Arnold, Lt. Comdr., USN
Larry J. Hines, Lt. Comdr., USN
Neill H. Baker, Maj., USAF
Robert B. Jamieson, Jr., Capt., USN
Mark T. Cenac, Maj., USA
Winston C. Jesseman, Lt. Col., USA

American Board of Surgery—Continued

Arthur Cohen, Lt. Col., USA
Donald G. Fahy, Lt. Col., USA
Robert J. Fleischaker, Comdr., USN
Philip O. Geib, Comdr., USN
Robert C. Laning, Lt. Comdr., USN
Edmund Scavone, Lt. Col., USA
Horace D. Warden, Capt., USN

Board of Thoracic Surgery

Philip L. Nova, Capt., USN

American Board of Anesthesiology

Basel M. Mixon, Jr., Maj., USA

American Board of Neurological Surgery

Joseph A. Witt, Lt. Comdr., USN

American Board of Periodontology

Wilfred B. Bell, Maj., USA
Herbert B. Lafitte, Lt. Col., USA

Central Repository for Medical Credentials

The Secretary General of The World Medical Association has announced that on 1 July 1958, the services of a Central Repository for Medical Credentials will become available to the doctors of the world. All judicious precautions will be exercised to protect the records of depositors.

During war and national uprisings, medical records are destroyed or lost. The plight of hundreds of doctors who fled from their homelands during World War II and the more recent Hungarian uprising stimulated The World Medical Association to undertake means assuring the doctor that he will always be able to prove himself medically trained and fully accredited to practice medicine. Today, many doctors are working as laborers or research assistants as a result of the loss or destruction of their original credentials and the lack of a protective service in which authenticated copies could be deposited.

The lifetime cost of the service on a one-payment basis to the newly graduated doctor is approximately $60.00 (USA). An actuarial schedule has been established for doctors in the various age groups. A 10-year service rate is also available.

The officials of the Repository recommend that doctors deposit their credentials in a form legally acceptable in the country or countries in which they would desire to establish themselves as qualified to practice medicine. It suggests that the credentials so deposited include official medical school record, medical diploma, and specialist credentials.

Additional information on the Central Repository for Medical Credentials is available from The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

AIR FORCE CONSULTANTS VISIT USAFE

Doctors Frank E. Stinchfield and Carlos G. de Gutierrez-Mahoney of New York City, national consultants to the Surgeon General of the Air Force, receive a briefing from Brigadier General Harold H. Twitchell, Surgeon of U. S. Air Forces in Europe. The consultants were accompanied last month on the tour of Air Force medical facilities in Europe by Colonel Frances Lay of Washington, Air Force Chief Nurse.

DEATHS

CHAFFIN, Alexander Nathan, Captain, MC, USN, of Wytheville, Va.; stationed at the Navy Preventive Medicine Unit Two, Naval Base, Norfolk, Va.; graduated in 1929 from the Medical College of Virginia, Richmond, Va.; served in an enlisted status in the United States Army from 17 October 1918 to 9 December 1918; appointed a lieutenant commander in the United States Naval Reserve 17 September 1942; ordered to active duty 2 November 1942; appointed a lieutenant commander in the United States Navy 25 June 1946; died 23 April 1958, age 58, at the U. S. Naval Hospital, Portsmouth, Va., of a pulmonary embolism.

GOFF, Harry Louis, Captain, MC, USN, of Chester, Pa.; stationed at the U. S. Naval Hospital, San Diego, Calif.; graduated in 1925 from the Jefferson Medical College of Philadelphia, Philadelphia, Pa., appointed a lieutenant (junior grade) in the United States Navy 4 June 1925; died 19 April 1958, age 59, at Del Mar, Calif., of coronary thrombosis.

HICKEY, William Thomas, Major, USAF (DC) of Daytona Beach, Fla.; stationed at the 7425th U. S. Air Force Hospital, APO 109, New York, N. Y.; graduated in 1947 from Northwestern University Dental School, Chicago, Ill.; commissioned a first lieutenant in the United States Air Force Reserve 4 December 1952; ordered to active duty 15 March 1953; died 2 April 1958, age 38, at Daytona Beach, Fla., of coronary thrombosis.

Reviews of Recent Books

A TEXTBOOK OF CLINICAL NEUROLOGY, With an Introduction to the History of Neurology, by *Israel S. Wechsler*, M. D. 8th edition. 782 pages; 179 illustrations, some in color. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $11.

This is the eighth edition of a book on clinical neurology which has enjoyed a rather widespread popularity on the American neurologic scene for the past 30 years. Nevertheless, in the opinion of this reviewer, the eighth edition is somewhat disappointing from the standpoint of being considered a major revision.

Although there are many excellent sections in this work, particularly the sections on neurosyphilis, epilepsy and aphasia, there are other sections which would seem to this reviewer somewhat sketchy for such a specialized textbook. While it is realized that the arrangement of a textbook is discretionary with an author; there are some aspects of this work which, in the opinion of this reviewer, would tend to confuse the student. An example of this is the listing of amyotrophic lateral sclerosis with the spinal cord diseases, and the lack of emphasis of the relation of this disease to progressive muscular atrophy, which is discussed in a section on neuromuscular disorders and myopathy. While many of the sections have been revised, many others are incomplete with regard to bibliographic references, which in some cases show no contributions later than 1948. In the case of amyotrophic lateral sclerosis and progressive muscular atrophy, for example, the work of Doctors Mulder and Kurland on the heredofamilial nature of these disorders has not been mentioned.

The heredofamilial disorders are rather sketchily treated and it is thought that their variants are discussed in insufficient detail considering the specialized nature of the material dealt with. Olivopontocerebellar atrophy is placed in a different section than heredofamilial disorders and the definite statement is made that this is not an hereditary condition, notwithstanding the fact that a family pedigree in which postmortem material, associated with clinical manifestations were discussed in which this disorder appeared as a clear-cut heredofamilial manifestation in a recent article.

While the section on syphilis of the nervous system is generally rather good, the discussion on tabes is described as an entity usually presenting little difficulty in diagnosis. This certainly is not in accord with the experience of most clinical neurologists these days. This disease is extremely subtle in its manifestations and because of its increasing rarity often presents an unusual degree of diagnostic difficulty, particularly in the absence of positive serologic reaction. In regard to diagnostic tests for syphilis, no mention is made of the importance of the use of the treponema immobilization procedure which has been shown to be of considerable aid in the diagnosis of doubtful cases. Fever therapy, which is recommended in this edition

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as being a desirable treatment of cases of general paresis is controversial at best.

In addition to the above criticism it is noted by this reviewer that there is a rather long section in the book devoted to a discussion of the neuroses, a feature which would seem to this reviewer rather anachronistic in a modern neurology textbook. This chapter is rather well written and, though rather long, can still hardly cover the ground adequately for the student of neurology. In the opinion of this reviewer, this space could have been much more profitably devoted to the expansion of some of the more purely neurologic sections of this book.

In summary, it is the belief of this reviewer that this volume will be accepted with considerable ambivalence by the specialty of neurology, particularly in view of Dr. Wechsler's significant contribution to the advancement of the study of neurology over the years as a clinician, teacher and author. Unfortunately, however, an objective evaluation of this work would seem to indicate that it does not come up to many of the textbooks on neurology which have been published here or in Great Britain during the past several years.

—ROY E. CLAUSEN, Jr., Lt. Col., MC, USA

5-HYDROXYTRYPTAMINE, Proceedings of a Symposium held in London on 1st and 2nd April, 1957, edited by *G. P. Lewis*, Ph. D. 253 pages; illustrated. Pergamon Press, New York, N. Y., 1958. Price $9.50.

This is a well-published and illustrated symposium of a remarkable meeting held to discuss the findings of research concerning 5-hydroxytryptamine.

In one sense, this small volume shows the evolution of thinking in a particular field of pharmacology. This field was introduced a number of years ago with the concept of sympathin E and sympathin I. In this symposium, the rapid evolution of such concepts is made apparent by use of the newly hypothesized trophotropic and ergotropic divisions of the autonomic nervous system. Regardless how controversial such a system is, it is a convenient scaffold on which may be built workable bits of research concerning the central and peripheral nervous systems.

The discussion of 5-hydroxytryptamine is thorough regarding its central and peripheral actions; however, all the discussions concern research animals. Nevertheless, any clinician may rapidly integrate this research material into a workable understanding of the causes of the symptoms accompanying this syndrome labeled "carcinoid."

This small publication will be most useful to researchers in the fields involving 5-hydroxytryptamine. All other physicians, however, should be aware of the scope of research involving exogenous and endogenous substances affecting the central nervous system. This volume should be included in all large medical libraries.

—EDWARD J. HUYCKE, Capt., MC, USA

PREVENTIVE MEDICINE FOR THE DOCTOR IN HIS COMMUNITY, An Epidemiologic Approach, by *Hugh Rodman Leavell,* M. D., Dr. P. H., and *E. Gurney Clark,* M. D., Dr. P. H., and 19 contributors. 2d edition. 689 pages. McGraw-Hill Book Co., Inc., The Blakiston Division, New York, N. Y., 1958. Price $10.

In this second edition the contributors have retained their purpose of presenting a text directed toward the development of a point of view, and the application of epidemiologic methodology to disease and accident prevention. Health promotion is emphasized. Chapters have been rearranged and grouped into three sections as follows: Basic Principles, Application of Principles, and Public Health-Preventive Medicine as Organized Community Action. The increasing importance of dentistry in health promotion and community health programs has been recognized by the inclusion of a new chapter on the Natural History and Prevention of Oral Disease. Many new diagrams and illustrations have been added and the text has been brought up-to-date.

Diseases, disorders and conditions are discussed with the concept in mind that they are the result of multiple causes acting through the agent, the host, and the environment. The natural history of the condition is presented, and application of preventive measures discussed. Such measures as health promotion and specific protection are applied at the prepathogenesis period; early diagnosis and prompt treatment, disability limitations, and rehabilitation are measures applied during the period of pathogenesis. The discussion of these concepts is made more lucid by well arranged diagrams.

One of the purposes of this book is to point out the value of practicing medicine with the preventive point of view and this is well done throughout. For the benefit of those who wish more detailed information references are provided at the end of each chapter, and a list for additional reading at the end of many.

This volume should be especially helpful to medical and dental students, practitioners and teachers of public health, and those general practitioners who wish to integrate preventive into the general practice of medicine. —*HOWARD K. SESSIONS, Capt., MC, USN*

PARENT-CHILD TENSIONS, by *Berthold Eric Schwarz,* M. D., and *Bartholomew A. Ruggieri,* M. D. 238 pages. J. B. Lippincott Co., Philadelphia, Pa., 1958. Price $4.95.

In "Parent-Child Tensions" Dr. Schwarz and Dr. Ruggieri have written an extremely interesting book on the problems of children. The first four chapters deal with the dynamics of normal emotional growth and development and are cleverly illustrated with quotes from suitable cases. In fact, the whole volume is rich with nontechnical, illustrative case material and reads like a popular book.

The next 12 chapters deal with specific psychiatric, psychosomatic and behavioral conditions such as enuresis, tics, temper tantrums,

asthma, various fears, delinquency and sexual problems. The remainder of the book is devoted to a variety of situations one encounters in pediatrics and practice in general, such as the child's emotions before and after surgery, emotional problems of handicapped children, feeblemindedness, death and divorce in the family and special problems regarding adoptions.

The authors are obviously well qualified and practical-minded specialists in pediatrics and psychiatry and have done an excellent job of combining their observations, experiences and treatment technics into a readable and nontechnical volume. It is intended in part as a "helpful guide for rearing well adjusted children," and has been recommended for physicians, parents and parents-to-be. The early chapters dealing with problems of the handicapped, death, divorce, et cetera may well serve that purpose, but I have strong personal reservations as to the usefulness of this book, or any book that attempts to give parents an understanding as to the role their own disturbed feelings play in the genesis of emotional disturbances in their children. We find that we are dealing usually with neurotic parents and intellectual explanations alone unfortunately are not very effective. It is hoped, however, that this book may influence the parents who need help in this field to seek it.

I enjoyed reading "Parent-Child Tensions" and compliment the authors on an informative as well as an enjoyable book. I recommend it to physicians, social workers, ministers, teachers, counselors, and with some reservations, to parents and parents-to-be.

—STEPHEN MOURAT, Lt. Col., MC, USA

THE BACTERIOLOGY OF TUBERCULOSIS, by *Egons Darzins*, M. D. 488 pages; illustrated. University of Minnesota Press, Minneapolis, Minn., 1958. Price $10.

This monograph presents an exhaustive survey of the literature of the bacteriology of tuberculosis from the late nineteenth century to the present day.

The objective of the author is to present a thorough understanding of the etiologic agent of tuberculosis so that the investigator may fix as his goal a complete conquest of the disease. Dr. Darzins has done this through a presentation of the material in historical sequence with an extensive bibliography consisting of abstracts from some 252 current periodicals.

This book is written primarily for the research specialist in tuberculosis bacteriology and as such is a shining example of scientific reporting. Because of its limited area it will not appeal to the Medical Officer in the field but should serve as a source-reference for the research worker, the investigator and the phthisiologist.

—CHIRISTOPHER C. SHAW, Capt., MC, USN

Symposium on DISEASES AND SURGERY OF THE LENS, Transactions of The New Orleans Academy of Ophthalmology, 1956, edited by *George M. Haik,* M. D., F. A. C. S., and *Elizabeth M. McFetridge,* M. A. Art Editor, *Don Alvarado.* 260 pages; illustrated. The C. V. Mosby Co., St. Louis, Mo., 1957. Price $10.50.

Modern ophthalmologic symposiums are performing a great service by making available to the practicing ophthalmologist current teaching of the masters in the diagnosis and management of various problems, and the Symposium on Diseases and Surgery of the Lens is an excellent example, published in book form.

The round-table discussions of problems in each disease category are very enjoyable and provide the answers to many questions which only mature judgement and experience can answer. The failure to include a section on the normal and pathologic physiology of the lens is regrettable but perhaps is circumstantial evidence that very little is known of this subject. This book should be a must for every resident and ophthalmic surgeon. —*JOSEPH M. JORDAN, Capt., MC, USN*

PRINCIPLES OF IMMUNOLOGY, by *John E. Cushing* and *Dan H. Campbell.* 344 pages; illustrated. McGraw-Hill Book Co., Inc., New York, N. Y., 1957. Price $6.50.

Immunity to disease has been the major stimulating factor in the development of the science of immunology. The technics and concepts of immunology, however, are not restricted to medicine and they provide a tool for the study of other biological problems: population genetics, embryological development, fertilization, and antigenic individuality. The authors of this book have focused their attention upon these latter problems, and have produced an extremely readable, interesting, and stimulating treatise. They have devoted eight pages, for example, to natural antibodies in humans, other vertebrates, invertebrates, and plants, but only a sentence to the more mundane Wassermann antibody.

The tremendous amount of information which the immune response has contributed to the attempted solution of biological problems has been assembled and interpreted in this book. Because it covers vast areas of the subject, experts in any particular field may not agree with some portions of the treatment made in the interest of simplification and condensation. Jerne's recent natural selection theory of antibody formation is stated merely to represent a revival of Ehrlich's receptor theory. That is partly true, but Jerne's theory goes much beyond Ehrlich's concept and has certain advantages over other current theories of antibody formation. This type of criticism could, of course, be leveled at almost any textbook.

Finally, this book is very valuable for students because it is characterized by an emphasis on principles rather than on the enumeration of data. Its excellent references to the original literature also enhance its value.—*LOUIS H. MUSCHEL, Maj., MSC, USA*

ACCEPTED DENTAL REMEDIES, 1958, Drugs used in Dental Practice including a List of Brands accepted by the Council on Dental Therapeutics of the American Dental Association. 23d edition. 214 pages. American Dental Association, Chicago, Ill., 1958. Price $2.

Less than half of this useful book deals directly with medicaments. The rest is a valuable, interesting account of allied factors in dental treatment; other sections are a pertinent and interesting account of allied factors in dental treatment. The chapter on "Dental Considerations of Patients Receiving Medical Care" is phrased in the language of a round-table discussion. It is a good exposition of current practices as opposed to outmoded textbook thinking. Another pertinent section concerns the "Treatment of Emergencies."

A section on "Nutrition" includes daily requirement charts and a bibliography. The accepted drugs are covered by description, action, uses and source. Those not approved, or with approval pending, also are listed. This review-reference volume is inexpensive, practical, and desirable.—*JULES D. KARTMAN, Lt. Col., USAF (DC)*

The Physiologic Basis of GASTROINTESTINAL THERAPY, Selected Topics, by *Heinrich Necheles,* M. D., Ph. D., F. A. C. P., and *Martin M. Kirshen,* M. D., F. A. C. P. 330 pages. Grune & Stratton, Inc., New York, N. Y., 1957. Price $8.75.

The authors of this slender volume believe that "The teaching of gastrointestinal physiology seems to be too cursory and inadequate. . . for the understanding of the disturbances of normal processes." They have, therefore, provided a review of the subject with emphasis on the physiologic alterations seen in disease states and the changes that may be brought about by therapy. The first half of the book contains chapters on innervation, motility, drug effects, secretion and digestion, and absorption and secretion. The latter portion covers ulcer, liver and gallbladder, and pancreas.

The style is readable, the material well presented. All important subjects are covered, and the correlation with clinical practice is excellent. This is not a textbook on physiology, however, and the discussions are presented as conclusions with very little background explanation or experimental data. No diagrams, chemical formulas, or illustrations interrupt the steady flow of concentrated, distilled description. There are many references included, so that if one wishes more detailed information, he will know where to find it.

At first glance, this brief, synoptic approach may seem disadvantageous. Few readers, however, would find the time to read a heavier, more exhaustive, and less conclusive text. This is a book for the medical student who needs to learn the relationship between the demonstrations in the laboratory and the symptoms of patients seen in the clinic. It is also a book for the practicing physician who needs to be reminded of the physiologic basis of many gastrointestinal complaints, and for all of us who need to be brought up to date on new developments and changing concepts.

—*BENJAMIN H. SULLIVAN, Jr., Col., MC, USA*

MOSBY'S REVIEW OF PRACTICAL NURSING, by *Dorothy Kelley Rapier*, R. N., B. S., et al. 2d edition. 354 pages; illustrated. The C. V. Mosby Co., St. Louis, Mo., 1957. Price $4.25.

This review will be of value for the practical nurse as preparation for licensing examinations if it is used as described by the authors, who state that "the material should be used in conjunction with textbooks or reference books." References from current texts are listed for each unit as an introduction after which there is a comprehensive outline of the entire unit as it is approached by the practical nurse. Following each unit, there are examination questions of various types: completion, matching, and multiple-choice questions, with answer sheets included. Since the technic of taking an objective examination can actually be the downfall for one who otherwise knows the subject, these examinations should be of assistance in directing the student's mental exercise and should serve as a stimulus and challenge to further study.

The units are tailored to the curriculum suggestions of the National Association of Practical Nurse Education and will be a consistent transition for the student to carry her thinking from a current accredited program on to the usual types of state registration examinations for practical nurses.

It is thought that there can be a definite hazard in the use of such a book by any other than one who is already qualified by a breadth of good learning experiences. For instance, in the unit Basic Nursing Care, it might be possible for one to assume the necessary knowledges of a procedure by only the four to five steps given in the outline when there is not the background realization of necessary precautions and understandings. This danger is also inherent in the unit on medications, of course.

There are a few unfortunate errors, for instance, the statement that the District of Columbia had licensing laws for practical nurses in 1955. There also are a few disturbing errors in outline format, and the detail in the outline on body structure is not reasonable for a practical nurse. It is believed that this book is of value for the specific group for which it is intended if it is used with intelligent discretion.

—*DELZENA E. GARRARD, Maj., ANC, USA*

PHARMACOLOGY AND THERAPEUTICS, A Textbook for Students and Practitioners of Medicine and Its Allied Professions, by *Arthur Grollman*, Ph. D., M. D., F. A. C. P. 3d edition. 1,046 pages; 192 illustrations, 2 in color; 35 tables. Lea & Febiger, Philadelphia, Pa., 1958. Price $12.50.

In the past several years two of the classic textbooks of pharmacology in this country have been revised. Grollman's new edition worthily places it in this category. The printing is superb, and it is pleasant to have a 1,000-page book which is not too heavy to hold and handle comfortably. The type face and the use of boldface letters make the text easy for both study and rapid scanning. It obviously

is written for medical students taking pharmacology in their first or second year. Therapeutic uses of the drugs discussed is very sketchy but reasonably well cross-indexed. The third edition is adequate in covering newer drugs such as tranquilizers and chemotherapeutic agents for malignancies, but it is difficult to understand why so much space is given to such drugs as strychnine and nicotine, while three short paragraphs are given to ethyl ether. Apparently, when the first pharmacology texts appeared the use of such drugs as strychnine and nicotine were mentioned at length to help define the physiologic and pharmacologic boundaries of drugs. Such autonomic studies are well discussed in general physiology now.

This text is not detailed enough nor does it give enough reference material to be useful in graduate teaching of pharmacology. At the end of each chapter is a list of USP drugs with their doses. The addendum to each chapter will be highly useful to house staff officers and practitioners because it should remind them that almost all pharmacologic agents can be secured from the USP listing.

The bibliography at the end of each chapter appears adequate for medical students and practitioners. This book is recommended for general medical libraries and medical students.

—*EDWARD J. HUYCKE, Capt., MC, USA*

THE YEAR BOOK OF DRUG THERAPY (1957-1958 Year Book Series), edited by *Harry Beckman*, M. D. 518 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $7.50.

This excellent collection of abstracts of the more important recent articles selected from American and foreign journals pertaining to drug therapy is well-organized and well-presented. Drug therapy in a wide variety of disease conditions is reviewed and current trends in therapy are described. The abstracts of the original articles contained in this book are brief, concise, accurate, clear, and are read with ease. Current experiences and trends in the treatment of various neoplastic diseases by drugs are discussed and recent concepts on the use of corticotropin and the cortisones are adequately reviewed. Various new antidiabetic drugs are discussed, presenting the methods and results of clinical employment as well as the mechanisms of action. The book summarizes current drug therapy for all major disease entities, particularly those in which there have been recent advances.

The references for the original articles abstracted in this book are conveniently printed as footnotes on the page on which the summary appears. Illustrations are black and white, and include graphs, charts, and photographs, which assist the reader in understanding the material.

This book is a necessity for all internists and general practitioners and is an excellent summary of the recent literature relating to drug therapy, and will serve as a source of ready reference for medical students. —*RALPH D. ROSS, Capt., MC, USN*

URINE AND THE URINARY SEDIMENT, A Practical Manual and Atlas, by *Richard W. Lippman,* B. S., M. D. 2d edition. 140 pages; 92 color photographs. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $8.50.

This is an excellent manual and atlas on urinary sediment, of special interest to those working in clinical laboratories and in the field of internal medicine. Urologists also can gain considerable information from it regarding the findings in urinary sediment. The first of three chapters covers proteinuria and elements of the urinary sediment; the second, clinical applications of the observations of the urine in disease; and the final chapter gives information regarding qualitative and simplified quantitative methods. While the author encourages the use of quantitative methods, it is recognized that qualitative means are necessary for practical screening purposes. Written in brief, terse descriptions this is a unique guide to the identification of formed elements in the urine and their significance. It is well illustrated and contains excellent colored microphotographs.

—*JOHN A. SCHINDLER, Col., USAF (MC)*

GENERAL DIAGNOSIS AND THERAPY OF SKIN DISEASES, An Introduction To Dermatology for Students and Physicians, by *Hermann Werner Siemens,* M. D. Translated from the German edition by *Kurt Wiener,* M. D. 324 pages; illustrated. The University of Chicago Press, Chicago, Ill., 1958. Price $10.

This is the first English translation of a German text, published originally in 1952. It is primarily a treatise on the fundamentals of dermatology. It is broadly divided into two sections, one on general diagnosis and the other on general principles of therapy.

The subject matter is handled in an informal narrative fashion and is not difficult reading. There is, however, a tremendous amount of information presented, much of it of practical importance. Most of the illustrations are close-ups and of unusual clarity.

One could make minor criticisms, such as too much splitting of hairs on minor details, and the introduction into an already overburdened dermatologic nomenclature additional synonyms for known entities. The author takes opportunity to proclaim four such synonyms, and in addition, labels them with his own name. This custom of adding eponyms to medical literature is not only unscientific, but actually harassing to medical advance.

This is not a book for an intern or the beginning resident. It should be required reading once every six months for the resident in dermatology. The two chapters on specific lesions, and extent, shape, and distribution of these lesions are worth the price of the book.

—*WILLIAM N. NEW, Capt., MC, USN*

MEDICAL DEPARTMENT, UNITED STATES ARMY, Surgery in World War II. Ophthalmology and Otolaryngology. Editor-in-Chief, Colonel *John Boyd Coates, Jr.*, MC, USA. Editor for Ophthalmology, *M. Elliott Randolph*, M. D. Editor for Otolaryngology, *Norton Canfield*, M. D. Associate Editor, *Elizabeth M. McFetridge*, M. A. 605 pages; illustrated. Historical Unit, Army Medical Service, Office of the Surgeon General, Department of the Army, Washington 25, D. C., 1957. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. Price $4.

This volume of "Surgery in World War II" devoted to ophthalmology and otolaryngology is a comprehensive volume about both specialties, during the war years. The book deals with the administrative aspects of ophthalmology and otolaryngology, and the problems faced by the administrator during an emergency of such magnitude as the war.

In the chapters devoted to ophthalmology, many of the problems peculiar to wartime practice are discussed. The civilian practitioner, often with limited experience in the military, was faced with problems of multiple intraocular foreign bodies, both magnetic and nonmagnetic; eye diseases peculiar to tropical conditions; nutritional amblyopia, as found in prisoners of war; and night blindness in service personnel.

One of the interesting features of the book is the history of development of the acrylic ocular prosthesis by the Dental Department. The contribution has been a big factor in our present-day use of ocular prosthesis of this nature.

In the otolaryngology section of the book, many of the problems of the otolaryngologist are discussed. Aside from the problems of administration, there was the constant casualty rate from acute pharyngitis, tonsillitis, and otitis media. Deafness in the combat soldier was a common occurrence, and much of the time of the otologist was devoted to audiometric studies and the rehabilitation of the deaf, through lip reading and hearing aids. Some outstanding work was performed on facial nerve paralysis by decompression and autogenous nerve grafts. The chapter devoted to plastic surgery of the ear, eye, nose, and throat is especially interesting.

The book is well worth reading from a historic as well as professional standpoint by both civilian and military specialists. It will give the reader some idea of the multiple problems faced by the military specialist in the administration, treatment, and disposition of the war casualty.

—*SHIRLEY A. FUHRING, Capt., MC, USN*

THE YEAR BOOK OF OPHTHALMOLOGY (1957-1958 Year Book Series), edited by *Derrick Vail*, B. A., M. D., D. Oph. (Oxon.), F. A. C. S., F. R. C. S. (Hon.) 423 pages; illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $7.50.

This is the first Year Book devoted exclusively to ophthalmology. Previous volumes for more than fifty years have been combined eye and ear, nose, and throat reviews. The separation into two volumes

has markedly benefited the ophthalmologic material, and has permitted more complete discussions of articles in the literature. The comments of the editor at the conclusion of many of the abstracts contribute much to the value of the book. He gives not only the benefit of his own wide experience but frequently quotes other recent pertinent literature as well. This feature alone would be worth the price of the book. In addition, this volume contains a 35-page lead article by Dr. Irving Leopold on "Recent Advances in Ocular Therapy." The book follows the same general topical outline as in previous editions. Desired material also is readily located through the use of separate indexes for subjects and authors. The book is not lavishly illustrated but it does contain photographs and diagrams when they are essential to ready comprehension of the abstracts. Literature of primarily research interest has not been included though this is being considered for future volumes.

Because of the extent of the literature which has been abstracted and the ease of quickly reviewing the latest information relating to a clinical condition, this is an invaluable book for the busy practicing ophthalmologist. It is equally useful to other professional specialists in the consideration of eye involvement in general diseases. For these reasons it should be a required volume in medical libraries.

—VICTOR A. BYRNES, Brig. Gen., USAF (MC)

GENERAL PATHOLOGY, based on Lectures delivered at the Sir William Dunn School of Pathology, University of Oxford, edited by Sir *Howard Florey*. 2d edition. 932 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $16.

The title of this volume is somewhat misleading in that this binding houses a series of monographs on various aspects of pathology and related subjects, rather than a complete discourse on the general aspects of pathology. These monographs are based on the lectures of Sir Howard and his associates and arranged as chapters in a logical sequence.

Subjects range from such standard titles as "History" and "Inflammation" to chapters on "Some Biological Effects of Radiant Energy" and "Biological Factors in the Production of Antibodies." Each unit is treated in a learned fashion, stressing pathologic physiology and avoiding the usual systematic descriptions of "dead house morphology." This approach, coupled together with a comprehensive style results in a refreshingly different attack on standard material.

The paper, print, binding, and illustrations are in keeping with the usual Saunders standards which combine ease of reading and durability. *—BRUCE H. SMITH, Jr., Capt., MC, USN*

UNEXPECTED REACTIONS TO MODERN THERAPEUTICS—ANTIBIOTICS, by *Leo Schindel,* M. D. 146 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $3.

This book deals with severe reactions to antibiotics and quotes reports from the literature concerning such reactions. No attempt is made to estimate the frequency of occurrence, but the author brings to mind the danger that exists in treatment by antibiotics. Because in a great many cases, even with a careful history, it was impossible to anticipate reactions, some serious but infrequent reactions from any antibiotic must be expected. The first part of the book deals with reactions to major antibiotics: penicillin with its skin reactions, serious allergic reactions to infinitesimal doses, and fatal anaphylactic shock; streptomycin's toxic effects on the eighth nerve, skin reactions, and encephalopathy; chloramphenicol's aplastic anemia, gastrointestinal and psychic symptoms; tetracyclines' allergic reactions, local mucosal changes with oral lozenges, the staphylococcal enteritis which may follow. There is a short chapter on antibiotic-resistant bacteria showing the rapidity with which the staphylococcus becomes resistant. The remainder is devoted to less frequently used antibiotics, neomycin, erythromycin, bacitracin, fumagillin, novobiocin, cycloserine, and polymyxin, all of which have their bad aspects. It is impossible to get an accurate estimate of the number of reactions to these drugs; the reports are scattered and many reactions are not reported. This book would be a useful addition to a medical library.

—*JAMES L. TOBIN, Col., USAF (MC)*

CEREBRAL LIPIDOSES, A Symposium. Chairman, *L. van Bogaert,* M. D. Editor, *J. N. Cumings,* M. D., F. R. C. P. Associate Editor, *A. Lowenthal,* M. D. 212 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $8.50.

According to the introduction by Doctor van Bogaert, an attempt is made to classify the lipidoses of the nervous system including their relationship to the subgroup of demyelinating diseases known as leukodystrophy. Also, another purpose is to check on the current value of histologic and histochemical methods in use in order to see if better procedures can be employed for more accurate information. Lastly, an effort to compare various quantitative methods from different laboratories is to be a goal so that the causes of obvious discrepancies can be determined.

A considerable portion of the book is centered in histochemical technics for determining the chemistry of the lipids concerned, purporting indications that leukodystrophy has a glycolipid which relates it to some of the primary lipidoses such as amaurotic idiocy. The whole question of myelin sheath formation is discussed from time to time.

No single classification of lipidoses offered in the book can be considered conclusive or final from a histologic or histochemical standpoint. L. Svennerholm pleads for exercise of caution in deriving conclusions about the chemical substrate of a disease from single

quantitative determinations or from mere histochemical investigations. He believes that the problems of study in neurolipidoses must be met on clinical, histopathologic and chemical grounds. In view of the above, the book does not provide a final answer to the classification of the lipidoses nor to their precise relationship to leukodystrophy but it does open further avenues of exploration. No doubt some benefit will be achieved by comparison of technics but this awaits clarification. On the whole, the book is rather erudite and esoteric. The book probably is best suited for those in neuropathology with special interest in the lipidoses and their histochemistry.

—*ARTHUR J. LEVENS, Lt. Col., MC, USA*

CLINICAL AND IMMUNOLOGIC ASPECTS OF FUNGOUS DISEASES, by *J. Walter Wilson*, M. D. American Lecture Series, Publication No. 324, a Monograph in The Bannerstone Division of American Lectures in Dermatology, edited by *Arthur C. Curtis*, M. D. 280 pages. Charles C Thomas, Publisher, Springfield, Ill., 1957. Price $6.75.

This interesting volume on fungous diseases should prove valuable to clinicians who are frequently perplexed by the variable manifestations of these diseases. The author relies heavily upon his own personal experiences with these diseases, extending over a 25-year-period, and his opinions and findings reflect his studious, personal approach. The format of 22 chapters without charts, graphs or illustrations, is unique and novel. The initial seven chapters are devoted to a comprehensive consideration of coccidioidomycosis as a guide in the study of infectious diseases. In subsequent chapters, the author repeatedly cites similarities or duplications of these phenomena in other mycotic diseases, enabling the reader to obtain at least a logical explanation for heretofore obscure mechanisms. The work is not intended as an encyclopedic textbook, but only as a supplement to the literature on certain aspects of fungous diseases. It is provocative, but easy reading and should, as the author hopes, stimulate others to a more exhaustive research and investigation in this field.

—*CLAUDE B. WHITE, Col., USAF (MC)*

SPINAL ANESTHESIA, by *John B. Dillon*, B. S., M. S., M. D. American Lecture Series, Publication No. 326, A Monograph in American Lectures in Anesthesiology, edited by *John Adriani*, M. D. 61 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $3.

This monograph of the author's method and technic in spinal anesthesia is very readable and can be digested leisurely in less than an hour. Consisting of 11 short chapters, it offers a successful method of surgical analygesia in selected cases. Ten illustrations show such fundamentals as positioning the patient, distribution of the somatic nerves, contour of the spinal column and dosage chart. It is not designed as a work of reference and would be of little benefit to the qualified anesthesiologist. The author proposes its use by "the physician who performs spinal anesthesia but who has had neither the time nor the opportunity to explore some of its facets."

—*ROBERT F. CORWIN, Col., USAF (MC)*

New Books Received

Books received by the *U. S. Armed Forces Medical Journal* are acknowledged in this department. Those of greatest interest will be selected for review in a later issue.

THE BRAIN AND HUMAN BEHAVIOR, Proceedings of the Association for Research in Nervous and Mental Disease, December 7 and 8, 1956, New York, N. Y. Editors: *Harry C. Solomon,* M. D.; *Stanley Cobb,* M. D.; and *Wilder Penfield,* M. D. 564 pages; with 200 illustrations and 53 tables. The Williams & Wilkins Co., Baltimore, Md., 1958. Price $15.

CLINICAL OBSTETRICS AND GYNECOLOGY, Volume 1, Number 1. A quarterly book series. Symposium on Medical Problems in Pregnancy, edited by *Curtis J. Lund,* M. D. Symposium on Management of Endocrine Problems, edited by *Allan C. Barnes,* M. D. 288 pages; illustrated. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York 16, N. Y., March 1958. Price: $18 for four consecutive numbers.

PSYCHOPROPHYLACTIC PREPARATION FOR PAINLESS CHILDBIRTH, Its theory and practical approach with the complete course of lectures, by *Isidore Bonstein,* M. D. 143 pages; illustrated. Grune & Stratton, Inc., New York, N. Y., 1958. Price $2.50.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, Volume 72, Art. 2, pages 69-126, March 17, 1958, editor-in-chief, *Otto V. St. Whitelock.* "The Paramagnetic Resonance and Optical Spectra," by *W. Low.* 57 pages; illustrated. The New York Academy of Sciences, New York, N. Y., 1958.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, Volume 72, Art. 3, pages 127-164, April 10, 1958, editor-in-chief, *Otto V. St. Whitelock.* "Recent Studies on the Epidemiology of Histoplasmosis," by *Michael L. Furcolow.* 37 pages; illustrated. The New York Academy of Sciences, New York, N. Y., 1958.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, Volume 72, Art. 4, pages 165-214, April 10, 1958, editor-in-chief, *Otto V. St. Whitelock.* "Man in Space: A Tool and Program for the Study of Social Change," by *Margaret Mead, Donald N. Michael, Harold D. Lasswell,* and *Lawrence K. Frank.* 49 pages. The New York Academy of Sciences, New York, N. Y., 1958.

THE MEDICAL WORLD OF THE EIGHTEENTH CENTURY, by *Lester S. King,* M. D. 346 pages. The University of Chicago Press, Chicago, Ill., 1958. Price $5.75.

SOCIAL CLASS AND MENTAL ILLNESS, A Community Study, by *August B. Hollingshead,* Ph. D., and *Fredrick C. Redlich,* M. D. 442 pages; illustrated. John Wiley and Sons, Inc., New York, N. Y., 1958. Price $7.50.

A SEARCH FOR MAN'S SANITY, The selected letters of Trigant Burrow, with biographical notes prepared by the *Editorial Committee of The Lifwynn Foundation: William E. Galt,* Chairman. Foreword by Sir *Herbert Read.* 615 pages. Oxford University Press, New York, N. Y., 1958. Price $8.75.

A TEXTBOOK OF DENTAL ANATOMY AND PHYSIOLOGY, by *Russell C. Wheeler,* D. D. S., F. A. C. D. 3d edition. 413 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $8.50.

GLAUCOMA, Transactions of the Second Conference, December 3, 4, and 5, 1956, Princeton, N. J., edited by *Frank W. Newell,* M. D. 245 pages; illustrated. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y., 1958. Price $4.95.

SYMPOSIUM ON RECENT CLINICAL ADVANCES—Pediatric Clinics of North America, May 1958. *Alan Ross,* M. D., Consulting Editor. 558 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958.

METHODS AND MATERIALS OF HEALTH EDUCATION, by *Robert E. Schneider,* M. S. P. H., Ed. D. 382 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $5.

A MANUAL OF DENTAL ANESTHESIA, An Illustrated Guide for Student and Practitioner, by *W. Harry Archer,* B. S., M. A., D. D. S. 2d edition. 346 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $8.50.

LABORATORY MEDICINE - HEMATOLOGY, by *John B. Miale,* M. D. 735 pages; 192 illustrations and 9 plates, including 5 in color. The C. V. Mosby Company, St. Louis, Mo., 1958. Price $13.75.

RECONSTRUCTIVE AND REPARATIVE SURGERY, by *Hans May,* M. D., F. A. C. S. 2d edition. 1,115 pages; with 1,030 illustrations, 55 in color. F. A. Davis Company, Philadelphia, Pa., 1958.

MEDICAL EMERGENCIES, Diagnosis and Treatment, By *Francis D. Murphy,* M. D., F. A. C. P., and Associate Authors. Foreword by *George Morris Piersol,* M. D. 6th edition. 635 pages; illustrated. F. A. Davis Company, Philadelphia, Pa., 1958.

THE MEDICAL MANAGEMENT OF CANCER, by *Henry D. Diamond,* M. D., F. A. C. P. 179 pages; illustrated. Grune and Stratton, Inc., New York, N. Y., 1958. Price $6.75.

ELECTRON MICROSCOPIC ATLAS OF NORMAL AND LEUKEMIC HUMAN BLOOD, by *Frank N. Low,* Ph. D., and *James A. Freeman.* 347 pages; illustrated. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, N. Y., 1958. Price $25.

INTRODUCTION TO MEDICAL SCIENCE, by *Gulli Lindh Muller,* M. D., and *Dorothy E. Dawes,* R. N., M. A. 4th edition. 606 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $5.50.

THE CHEMISTRY AND CHEMOTHERAPY OF TUBERCULOSIS, A compilation and critical review of existing knowledge on the chemistry of tubercle bacilli and their products, chemical changes and processes in the host, and chemical aspects of the treatment of tuberculosis, by *Esmond R. Long,* M. D., Ph. D., Sc. D. 3d edition. 450 pages; illustrated. The Williams & Wilkins Co., Baltimore, Md., 1958. Price $12.

HANDBOOK OF TREATMENT OF ACUTE POISONING, by *E. H. Bensley,* M. B. E., B. A., M. D., F. A. C. P., and *G. E. Joron,* B. A., M. D., C. M., F. A. C. P. 2d edition. 212 pages. E. & S. Livingstone Ltd., Edinburgh and London, 1958. The Williams & Wilkins Co., Baltimore, Md., exclusive U. S. agents. Price $4.

INTESTINAL OBSTRUCTION, by *Claude E. Welch,* M. D., D. Sc. (Hon.). Illustrated by *Muriel McLatchie Miller.* 376 pages. The Year Book Publishers, Inc., Chicago, Ill., 1958. Price $10.50.

DYNAMIC ANATOMY AND PHYSIOLOGY, by *L. L. Langley,* Ph. D., LL. B.; *E. Cheraskin,* M. D., D. M. D.; and *Ruth Sleeper,* R. N. 719 pages; illustrated. The Blakiston Division, McGraw-Hill Book Company, Inc., New York, N. Y., 1958. Price $6.

TEACHING PHYSICAL EDUCATION IN ELEMENTARY SCHOOLS, by *Maryhelen Vannier*, Ed. D., and *Mildred Foster*, B. S. 2d edition. 368 pages; illustrated. W. B. Saunders Co., Philadelphia, Pa., 1958. Price $4.75.

THE CHEMICAL DYNAMICS OF BONE MINERAL, by *William F. Neuman* and *Margaret W. Neuman*. 209 pages; illustrated. The University of Chicago Press, Chicago, Ill., 1958. Price $5.

FUNCTIONAL BRACING OF THE UPPER EXTREMITIES, edited by *Raymond E. Solars*. Written and illustrated by *Miles H. Anderson*, Ed. D. Foreword by *Charles O. Bechtol*, M. D. 463 pages; illustrated. Charles C Thomas, Publisher, Springfield, Ill., 1958. Price $9.50.

DRUGS OF CHOICE (1958-1959), edited by *Walter Modell*, M. D. 931 pages; illustrated. The C. V. Mosby Co., St. Louis, Mo., 1958. Price $12.75.

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